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 (approx. 18 x 6 mm) 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 (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

4.2 Posology and method of administration

Posology

Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole. Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food. Pradaxa powder and solvent for oral solution should only be used in children aged less than 1 year.

When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

Primary prevention of VTE in orthopaedic surgery

The recommended doses of dabigatran etexilate and the duration of therapy for primary prevention of VTE in orthopaedic surgery are shown in table 1.
Table 1: Dose recommendations and duration of therapy for primary prevention of VTE in orthopaedic surgery

<table>
<thead>
<tr>
<th>Patients following elective knee replacement surgery</th>
<th>Treatment initiation on the day of surgery</th>
<th>Maintenance dose starting on the first day after surgery</th>
<th>Duration of maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-4 hours after completed surgery</td>
<td>220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg</td>
<td>10 days</td>
</tr>
<tr>
<td></td>
<td>single capsule of 110 mg dabigatran etexilate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients following elective hip replacement surgery</td>
<td></td>
<td>220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg</td>
<td>28-35 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reduction recommended</td>
<td></td>
<td>220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg</td>
<td>10 days</td>
</tr>
<tr>
<td>Patients with moderate renal impairment (CrCl 30-50 mL/min)</td>
<td>single capsule of 75 mg dabigatran etexilate</td>
<td></td>
<td>(knee replacement surgery)</td>
</tr>
<tr>
<td>Patients who receive concomitant verapamil*, amiodarone, quinidine</td>
<td>150 mg dabigatran etexilate once daily taken as 2 capsules of 75 mg</td>
<td>10 days (knee replacement surgery) or 28-35 days (hip replacement surgery)</td>
<td></td>
</tr>
<tr>
<td>Patients aged 75 or above</td>
<td></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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate at the same time of the next day.

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

**Discontinuation of dabigatran etexilate**

Dabigatran etexilate 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

Dabigatran etexilate treatment to parenteral anticoagulant:
It is recommended to wait 24 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate in the paediatric population for the indication of primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Treatment of VTE and prevention of recurrent VTE in paediatric patients

For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.
Dabigatran etexilate capsules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate capsules is based on the patient’s weight and age as shown in table 2. The dose should be adjusted according to weight and age as treatment progresses.

For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 2: Single and total daily dabigatran etexilate doses in milligrams (mg) by weight in kilograms (kg) and age in years of the patient

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Age in years</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to &lt;13</td>
<td>8 to &lt;9</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>13 to &lt;16</td>
<td>8 to &lt;11</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>16 to &lt;21</td>
<td>8 to &lt;14</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>21 to &lt;26</td>
<td>8 to &lt;16</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>26 to &lt;31</td>
<td>8 to &lt;18</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>31 to &lt;41</td>
<td>8 to &lt;18</td>
<td>185</td>
<td>370</td>
</tr>
<tr>
<td>41 to &lt;51</td>
<td>8 to &lt;18</td>
<td>220</td>
<td>440</td>
</tr>
<tr>
<td>51 to &lt;61</td>
<td>8 to &lt;18</td>
<td>260</td>
<td>520</td>
</tr>
<tr>
<td>61 to &lt;71</td>
<td>8 to &lt;18</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>71 to &lt;81</td>
<td>8 to &lt;18</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>&gt;81</td>
<td>10 to &lt;18</td>
<td>300</td>
<td>600</td>
</tr>
</tbody>
</table>

Single doses requiring combinations of more than one capsule:
- 300 mg: two 150 mg capsules or four 75 mg capsules
- 260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
- 220 mg: as two 110 mg capsules
- 185 mg: as one 75 mg plus one 110 mg capsule
- 150 mg: as one 150 mg capsule or two 75 mg capsules

Assessment of renal function prior to and during treatment

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).

Treatment with dabigatran etexilate in paediatric patients with eGFR <50 mL/min/1.73m² is contraindicated (see section 4.3).

Patients with an eGFR ≥50 mL/min/1.73m² should be treated with the dose according to table 2.

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

Duration of use

The duration of therapy should be individualised based on the benefit risk assessment.
Missed dose

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. A double dose to make up for missed individual doses must never be taken.

Discontinuation of dabigatran etexilate

Dabigatran etexilate treatment should not be discontinued without medical advice. Patients or their caregivers should be instructed to contact the treating physician if the patient develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

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

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):
Patients should start VKA 3 days before discontinuing dabigatran etexilate.
Because dabigatran etexilate can impact the international normalised ratio (INR), the INR will better reflect VKA’s effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

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

Method of administration

This medicinal product is for oral use. The capsules can be taken with or without food. The capsules 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
- Severe renal impairment (CrCL <30 mL/min) in adult patients
- eGFR <50 mL/min/1.73m² in paediatric patients
- 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. These are switching anticoagulant therapy (see section 4.2), when UFH is given at doses
necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (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, droledrone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Dabigatran etexilate 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. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For adults patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent idarucizumab is available. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also 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 3 summarises factors which may increase the haemorrhagic risk.

**Table 3: Factors which may increase the haemorrhagic risk.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacodynamic and kinetic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Factors increasing dabigatran plasma levels</td>
<td>Major:</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor:</td>
</tr>
<tr>
<td>Pharmacodynamic interactions (see section 4.5)</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases / procedures with special haemorrhagic risks</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
defects
- Recent biopsy, major trauma
- Bacterial endocarditis
- Esophagitis, gastritis or gastroesophageal reflux

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

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

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. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected 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 dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5).

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

Discontinuation of dabigatran etexilate

Patients who develop acute renal failure must discontinue dabigatran etexilate (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 (idarucizumab) may be considered in adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Use of proton-pump inhibitors

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding. In case of paediatric patients local labeling recommendations for proton pump inhibitors have to be followed.
Laboratory coagulation parameters

Although this medicinal product 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 dabigatran etexilate and false positive INR elevations have been reported. Therefore INR tests should not be performed.

Table 4 shows coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding. Respective thresholds for paediatric patients are not known (see section 5.1).

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

<table>
<thead>
<tr>
<th>Test (trough value)</th>
<th>Threshold</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 dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate.

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

Emergency surgery or urgent procedures

Dabigatran etexilate should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (idarucizumab) to dabigatran is available for adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.
**Subacute surgery/interventions**

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

**Elective surgery**

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

Table 5 summarises discontinuation rules before invasive or surgical procedures for adult patients.

**Table 5: Discontinuation rules before invasive or surgical procedures for adult patients**

<table>
<thead>
<tr>
<th>Renal function (CrCL in mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Dabigatran etexilate should be stopped before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80</td>
<td>~ 13</td>
<td>2 days before</td>
</tr>
<tr>
<td>50–80</td>
<td>~ 15</td>
<td>2-3 days before</td>
</tr>
<tr>
<td>≥30–50</td>
<td>~ 18</td>
<td>4 days before</td>
</tr>
</tbody>
</table>

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 6.

**Table 6: Discontinuation rules before invasive or surgical procedures for paediatric patients**

<table>
<thead>
<tr>
<th>Renal function (eGFR in mL/min/1.73m²)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>24 hours before</td>
</tr>
<tr>
<td>50 – 80</td>
<td>2 days before</td>
</tr>
<tr>
<td>&lt;50</td>
<td>These patients have not been studied (see section 4.3).</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 dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

**Postoperative phase**

Dabigatran etexilate 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 reduced renal function (see also table 3), 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 dabigatran etexilate available in these patients and therefore they should be treated with caution.
Hip fracture surgery
There is no data on the use of dabigatran etexilate 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 dabigatran etexilate 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).

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Active cancer patients (paediatric VTE)
There is limited data on efficacy and safety for paediatric patients with active cancer.

Paediatric population
For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

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>Concomitant use contraindicated (see section 4.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</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</td>
</tr>
</tbody>
</table>
When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC<sub>0-∞</sub> and C<sub>max</sub> 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.

Based on <i>in vitro</i> results a similar effect as with ketoconazole may be expected.

The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.

Concomitant use not recommended

Tacrolimus has been found <i>in vitro</i> 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)

When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C<sub>max</sub> 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<sub>max</sub> by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.

When dabigatran etexilate 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<sub>max</sub> 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 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<sup>rd</sup> day either with or without quinidine. Dabigatran AUC<sub>τ,ss</sub> and C<sub>max,ss</sub> were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4).

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<sub>max</sub> by about 1.15-fold was observed.

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<sub>max</sub> 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<sub>max</sub> and AUC, respectively.
Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{ss}$ 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 $AUC_{ss}$ 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 $AUC_{ss}$ and $C_{max,ss}$ 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 dabigatran etexilate 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 dabigatran etexilate.

P-gp substrate

Digoxin

In a study performed with 24 healthy subjects, when dabigatran etexilate 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 dabigatran etexilate: 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 or during catheter ablation for atrial fibrillation (see section 4.3).

### Table 8: Interactions with anticoagulants and antiplatelet aggregation medicinal products

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Interaction Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>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 a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY), NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin.</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></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_{τ,ss} and C_{max,ss} and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran AUC_{τ,ss} and C_{max,ss} were increased by about 30-40 % (see section 4.4).</td>
</tr>
<tr>
<td><strong>ASA</strong></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><strong>LMWH</strong></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>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Interaction Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</strong></td>
<td>SSRIs, 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).</td>
</tr>
<tr>
<td><strong>Substances influencing gastric pH</strong></td>
<td>Pantoprazole</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</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.

Paediatric population

Interaction studies have only been performed in adults.

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

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

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate.

In actively controlled VTE prevention trials 6,684 patients were treated with 150 mg or 220 mg dabigatran etexilate 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 10 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 10: 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>Neutropenia</td>
<td>Not known</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</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>Abdominal pain</td>
<td>Rare</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Rare</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
</tbody>
</table>
Hepatic function abnormal/ Liver function Test abnormal

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</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>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemarthrosis</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Renal and urinary disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourlogical haemorrhage, including haematuria</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Site Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site haemorrhage</td>
<td>Rare</td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Rare</td>
</tr>
<tr>
<td>Bloody discharge</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Injury, poisoning and procedural complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural discharge</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Wound secretion</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Rare</td>
</tr>
<tr>
<td>Anaemia postoperative</td>
<td>Rare</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>Rare</td>
</tr>
<tr>
<td>Wound drainage</td>
<td>Rare</td>
</tr>
<tr>
<td>Post procedural drainage</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of dabigatran etexilate 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 dabigatran etexilate 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 and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. For adult patients, a specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

The table 11 shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the indication primary VTE prevention after hip or knee replacement surgery in the two pivotal clinical trials, according to dose.
Table 11: Number (%) of patients experiencing the adverse reaction bleeding

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 150 mg N (%)</th>
<th>Dabigatran etexilate 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>

**Agranulocytosis and neutropenia**

Agranulocytosis and neutropenia have been reported very rarely during post approval use of dabigatran etexilate. Because adverse reactions are reported in the postmarketing surveillance setting from a population of uncertain size, it is not possible to reliably determine their frequency. The reporting rate was estimated as 7 events per 1 million patient years for agranulocytosis and as 5 events per 1 million patient years for neutropenia.

**Paediatric population**

The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

**Tabulated list of adverse reactions**

Table 12 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. 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 12: Adverse reactions

<table>
<thead>
<tr>
<th>SOC / Preferred term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment of VTE and prevention of recurrent VTE in paediatric patients</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Common</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Not known</td>
</tr>
<tr>
<td>Disorder</td>
<td>Frequency</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Common</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Common</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td>Not known</td>
</tr>
<tr>
<td>Gastroesophagitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/liver function Test abnormal</td>
<td>Not known</td>
</tr>
<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>Common</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Genitouriological haemorrhage, including haematuria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
</tr>
<tr>
<td>Traumatic haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Not known</td>
</tr>
</tbody>
</table>

*Bleeding reactions*

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.
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

Dabigatran etexilate 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 dabigatran etexilate 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, dabigatran etexilate 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 adult patients in situations when rapid reversal of the anticoagulant effect of dabigatran is required the specific reversal agent (idarucizumab) antagonizing the pharmacodynamic effect of dabigatran is available. The efficacy and safety of idarucizumab have not been established in paediatric patients (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.

Primary prevention of VTE 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.

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 VTE prophylaxis following major joint replacement surgery

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

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

Composite of total VTE (including pulmonary embolism (PE), proximal and distal deep vein thrombosis (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 220 mg and 150 mg dabigatran etexilate 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 13). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 13).

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 13.

Data for the total VTE and all cause mortality endpoint are shown in table 14.

Data for adjudicated major bleeding endpoints are shown in table 15 below.
Table 13: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

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

Table 14: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg</th>
<th>Dabigatran etexilate 150 mg</th>
<th>Enoxaparin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (hip)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>880</td>
<td>874</td>
<td>897</td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>53 (6.0)</td>
<td>75 (8.6)</td>
<td>60 (6.7)</td>
</tr>
<tr>
<td>Risk ratio over enoxaparin</td>
<td>0.9</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>95 % CI</td>
<td>(0.63, 1.29)</td>
<td>(0.93, 1.78)</td>
<td></td>
</tr>
<tr>
<td>RE-MODEL (knee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>503</td>
<td>526</td>
<td>512</td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>183 (36.4)</td>
<td>213 (40.5)</td>
<td>193 (37.7)</td>
</tr>
<tr>
<td>Risk ratio over 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 15: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg</th>
<th>Dabigatran etexilate 150 mg</th>
<th>Enoxaparin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (hip)</td>
<td></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>

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

Clinical trials in VTE prophylaxis following major joint replacement surgery

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 indication of primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery (see section 4.2 for information on paediatric use).

Treatment of VTE and prevention of recurrent VTE in paediatric patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.

In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.

Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.

Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate group and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major
and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee. Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

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 characterised 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 16.

**Special populations**

**Renal insufficiency**

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

In a small number of adult 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>
<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 randomised 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 adult 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 \( C_{\text{max}} \) 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 adult 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 adult 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 adult 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.

**Paediatric population**
Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT / PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to <2-year-old, 2 to <12-year-old and 12 to <18-year-old paediatric VTE patients, respectively.

**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 a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile
rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

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
Hypromellose
Dimeticone 350
Talc
Hydroxypropylecelulose

Capsule shell
Carrageenan
Potassium chloride
Titanium dioxide
Hypromellose

Black printing ink
Shellac
Iron oxide black
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

Perforated aluminium unit dose blisters of 10 x 1 hard capsules. Each carton contains 10, 30 or 60 hard capsules.

Perforated aluminium unit dose white blisters of 10 x 1 hard capsules. Each carton contains 60 hard capsules.

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
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 AUTHORISATION

Date of first authorisation: 18 March 2008
Date of latest renewal: 08 January 2018
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 (approx. 19 x 7 mm) 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 (VTE) 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.
   Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.
   For age appropriate dose forms, see section 4.2.

   4.2 Posology and method of administration
   Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole. Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food. Pradaxa powder and solvent for oral solution should only be used in children aged less than 1 year.
   When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

   Primary prevention of VTE in orthopaedic surgery
   The recommended doses of dabigatran etexilate and the duration of therapy for primary prevention of VTE in orthopaedic surgery are shown in table 1.
Table 1: Dose recommendations and duration of therapy for primary prevention of VTE in orthopaedic surgery

<table>
<thead>
<tr>
<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 dabigatran etexilate</td>
<td>230 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg</td>
</tr>
<tr>
<td>Patients following elective hip replacement surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dose reduction recommended**

| Patients with moderate renal impairment (CrCl 30-50 mL/min) | single capsule of 75 mg dabigatran etexilate | 150 mg dabigatran etexilate once daily taken as 2 capsules of 75 mg | 10 days (knee replacement surgery) or 28-35 days (hip replacement surgery) |
| Patients who receive concomitant verapamil*, amiodarone, quinidine | | | |
| Patients aged 75 or above | | | |

*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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate at the same time of the next day.

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

*Discontinuation of dabigatran etexilate*

Dabigatran etexilate 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

Dabigatran etexilate treatment to parenteral anticoagulant:
It is recommended to wait 24 hours after the last dose before switching from dabigatran etexilate to a
parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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
dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate in the paediatric population for the indication of
primary prevention of VTE 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 DVT and PE and prevention of recurrent DVT and PE in adults (DVT/PE)**

The recommended doses of dabigatran etexilate 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>Dose recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)</td>
</tr>
<tr>
<td>300 mg dabigatran etexilate taken as one 150 mg capsule twice daily</td>
</tr>
<tr>
<td>Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (DVT/PE)</td>
</tr>
<tr>
<td>300 mg dabigatran etexilate taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days</td>
</tr>
<tr>
<td>Dose reduction recommended</td>
</tr>
<tr>
<td>Patients aged ≥80 years</td>
</tr>
<tr>
<td>daily dose of 220 mg dabigatran etexilate taken as one 110 mg capsule twice daily</td>
</tr>
<tr>
<td>Patients who receive concomitant verapamil</td>
</tr>
<tr>
<td>Dose reduction for consideration</td>
</tr>
<tr>
<td>Patients between 75-80 years</td>
</tr>
<tr>
<td>Patients with moderate renal impairment (CrCL 30-50 mL/min)</td>
</tr>
<tr>
<td>daily dose of dabigatran etexilate 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>
</tr>
<tr>
<td>Other patients at increased risk of bleeding</td>
</tr>
</tbody>
</table>

For DVT/PE the recommendation for the use of 220 mg dabigatran etexilate 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 dabigatran etexilate, 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.

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

**Discontinuation of dabigatran etexilate**

Dabigatran etexilate 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**

Dabigatran etexilate treatment to parenteral anticoagulant:

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

Parenteral anticoagulants to dabigatran etexilate:

The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate 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 dabigatran etexilate
- CrCL ≥30-<50 mL/min, VKA should be started 2 days before discontinuing dabigatran etexilate

Because dabigatran etexilate can impact the International Normalised Ratio (INR), the INR will better reflect VKA’s effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.
VKA to dabigatran etexilate:
The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is <2.0.

**Cardioversion (SPAF)**

Patients can stay on dabigatran etexilate while being cardioverted.

**Catheter ablation for atrial fibrillation (SPAF)**

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

**Percutaneous coronary intervention (PCI) with stenting (SPAF)**

Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with dabigatran etexilate in combination with antiplatelets after haemostasis is achieved (see section 5.1).

**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 dabigatran etexilate 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 dabigatran etexilate is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate in the paediatric population for the indication of prevention of stroke and systemic embolism in patients with NVAF.

Treatment of VTE and prevention of recurrent VTE in paediatric patients

For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.

Dabigatran etexilate capsules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate capsules is based on the patient’s weight and age as shown in table 4. The dose should be adjusted according to weight and age as treatment progresses.

For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 4: Single and total daily dabigatran etexilate doses in milligrams (mg) by weight in kilograms (kg) and age in years of the patient

<table>
<thead>
<tr>
<th>Weight /age combinations</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to &lt;13</td>
<td>8 to &lt;9</td>
<td>75</td>
</tr>
<tr>
<td>13 to &lt;16</td>
<td>8 to &lt;11</td>
<td>110</td>
</tr>
<tr>
<td>16 to &lt;21</td>
<td>8 to &lt;14</td>
<td>110</td>
</tr>
<tr>
<td>21 to &lt;26</td>
<td>8 to &lt;16</td>
<td>150</td>
</tr>
<tr>
<td>26 to &lt;31</td>
<td>8 to &lt;18</td>
<td>150</td>
</tr>
<tr>
<td>31 to &lt;41</td>
<td>8 to &lt;18</td>
<td>185</td>
</tr>
<tr>
<td>41 to &lt;51</td>
<td>8 to &lt;18</td>
<td>220</td>
</tr>
<tr>
<td>51 to &lt;61</td>
<td>8 to &lt;18</td>
<td>260</td>
</tr>
<tr>
<td>61 to &lt;71</td>
<td>8 to &lt;18</td>
<td>300</td>
</tr>
<tr>
<td>71 to &lt;81</td>
<td>8 to &lt;18</td>
<td>300</td>
</tr>
<tr>
<td>≥81</td>
<td>10 to &lt;18</td>
<td>300</td>
</tr>
</tbody>
</table>

Single doses requiring combinations of more than one capsule:

- 300 mg: two 150 mg capsules or four 75 mg capsules
- 260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
- 220 mg: as two 110 mg capsules
- 185 mg: as one 75 mg plus one 110 mg capsule
- 150 mg: as one 150 mg capsule or two 75 mg capsules
**Assessment of renal function prior to and during treatment**

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).

Treatment with dabigatran etexilate in paediatric patients with eGFR \(< 50 \text{ mL/min}/1.73\text{m}^2\) is contraindicated (see section 4.3).

Patients with an eGFR \( \geq 50 \text{ mL/min}/1.73\text{m}^2\) should be treated with the dose according to table 4.

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

**Duration of use**

The duration of therapy should be individualised based on the benefit risk assessment.

**Missed dose**

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. A double dose to make up for missed individual doses must never be taken.

**Discontinuation of dabigatran etexilate**

Dabigatran etexilate treatment should not be discontinued without medical advice. Patients or their caregivers should be instructed to contact the treating physician if the patient develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

**Switching**

Dabigatran etexilate treatment to parenteral anticoagulant:

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

Parenteral anticoagulants to dabigatran etexilate:

The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):

Patients should start VKA 3 days before discontinuing dabigatran etexilate. Because dabigatran etexilate can impact the International Normalised Ratio (INR), the INR will better reflect VKA’s effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to dabigatran etexilate:

The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is <2.0.

**Method of administration**

This medicinal product is for oral use. The capsules can be taken with or without food. The capsules 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
- Severe renal impairment (CrCL <30 mL/min) in adult patients
- eGFR <50 mL/min/1.73m² in paediatric patients
- 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. These are switching anticoagulant therapy (see section 4.2), when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Dabigatran etexilate 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. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent idarucizumab is available. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also section 4.9).

In clinical trials, dabigatran etexilate 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 5) 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 5 summarises factors which may increase the haemorrhagic risk.

**Table 5: Factors which may increase the haemorrhagic risk.**

<table>
<thead>
<tr>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacodynamic and kinetic factors</strong></td>
</tr>
<tr>
<td><strong>Factors increasing dabigatran plasma levels</strong></td>
</tr>
<tr>
<td>Major:</td>
</tr>
<tr>
<td>- Moderate renal impairment in adult patients (30-50 mL/min CrCL)</td>
</tr>
<tr>
<td>- Strong P-gp inhibitors (see section 4.3 and 4.5)</td>
</tr>
<tr>
<td>- Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5)</td>
</tr>
<tr>
<td>Minor:</td>
</tr>
<tr>
<td>- Low body weight (&lt;50 kg) in adult patients</td>
</tr>
<tr>
<td><strong>Pharmacodynamic interactions (see section 4.5)</strong></td>
</tr>
<tr>
<td>- ASA and other platelet aggregation inhibitors such as clopidogrel</td>
</tr>
<tr>
<td>- NSAIDs</td>
</tr>
<tr>
<td>- SSRIs or SNRIs</td>
</tr>
<tr>
<td>- Other medicinal products which may impair haemostasis</td>
</tr>
<tr>
<td><strong>Diseases / procedures with special haemorrhagic risks</strong></td>
</tr>
<tr>
<td>- Congenital or acquired coagulation disorders</td>
</tr>
<tr>
<td>- Thrombocytopenia or functional platelet defects</td>
</tr>
<tr>
<td>- Recent biopsy, major trauma</td>
</tr>
<tr>
<td>- Bacterial endocarditis</td>
</tr>
<tr>
<td>- Esophagitis, gastritis or gastroesophageal reflux</td>
</tr>
</tbody>
</table>

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

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

**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. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected 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 5 above). Particular caution should be exercised when dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5). Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).

Discontinuation of dabigatran etexilate

Patients who develop acute renal failure must discontinue dabigatran etexilate (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 (idarucizumab) may be considered in adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Use of proton-pump inhibitors

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding. In case of paediatric patients local labeling recommendations for proton pump inhibitors have to be followed.

Laboratory coagulation parameters

Although this medicinal product 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 dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Table 6 shows coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding. Respective thresholds for paediatric patients are not known (see section 5.1).

Table 6: Coagulation test thresholds at trough for adult patients 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>&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 dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Patients can stay on dabigatran etexilate while being cardioverted. There are no data available for 110 mg twice daily dabigatran etexilate 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

Dabigatran etexilate should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (idarucizumab) to dabigatran is available for adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

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

Subacute surgery/interventions

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

Elective surgery

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

Table 7 summarises discontinuation rules before invasive or surgical procedures for adult patients.

<table>
<thead>
<tr>
<th>Renal function (CrCL in mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Dabigatran etexilate 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>

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 8.

Table 8: Discontinuation rules before invasive or surgical procedures for paediatric patients

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function</td>
<td>Stop dabigatran before elective surgery</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 dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

### Postoperative phase

Dabigatran etexilate treatment should be resumed / started 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 reduced renal function (see also table 5), 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 dabigatran etexilate available in these patients and therefore they should be treated with caution.

### Hip fracture surgery

There is no data on the use of dabigatran etexilate 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 dabigatran etexilate 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).

### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.
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, paediatric VTE)
The efficacy and safety have not been established for DVT/PE patients with active cancer. There is limited data on efficacy and safety for paediatric patients with active cancer.

Paediatric population

For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

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 9) 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 9: 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_{0-∞} and C_{max} 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_{0-∞} and C_{max} 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</td>
<td>Based on in vitro results a similar effect as with ketoconazole may be expected.</td>
</tr>
<tr>
<td>Drug</td>
<td>Effect Description</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.</td>
</tr>
<tr>
<td><strong>Concomitant use not recommended</strong></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</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>Verapamil</td>
<td>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.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>When dabigatran etexilate 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$<em>{\text{τ,ss}}$ 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 $C_{\text{max}}$ 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$<em>{\text{τ,ss}}$ 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$<em>{\text{τ,ss}}$ and $C</em>{\text{max,ss}}$ was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone.</td>
</tr>
</tbody>
</table>
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$_{τ,ss}$ and C$_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

<table>
<thead>
<tr>
<th>Posaconazole</th>
<th>Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when dabigatran etexilate is co-administered with posaconazole.</th>
</tr>
</thead>
</table>

**P-gp inducers**

Concomitant use should be avoided.

<table>
<thead>
<tr>
<th>e.g. rifampicin, St. John’s wort (Hypericum perforatum), carbamazepine, or phenytoin</th>
<th>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.</th>
</tr>
</thead>
</table>

**Protease inhibitors such as ritonavir**

Concomitant use not recommended

<table>
<thead>
<tr>
<th>e.g. ritonavir and its combinations with other protease inhibitors</th>
<th>These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran etexilate.</th>
</tr>
</thead>
</table>

**P-gp substrate**

<table>
<thead>
<tr>
<th>Digoxin</th>
<th>In a study performed with 24 healthy subjects, when dabigatran etexilate was co-administered with digoxin, no changes on digoxin and no clinically relevant changes on dabigatran exposure have been observed.</th>
</tr>
</thead>
</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 dabigatran etexilate: 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 sulfinpyrazone (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 or during catheter ablation for atrial fibrillation (see section 4.3).

Table 10: Interactions with anticoagulants and antiplatelet aggregation medicinal products

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Interaction Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></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\textsubscript{τ,ss} and C\textsubscript{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{τ,ss} and C\textsubscript{max,ss} were increased by about 30-40% (see section 4.4).</td>
</tr>
<tr>
<td><strong>ASA</strong></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><strong>LMWH</strong></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 11: Other interactions

<table>
<thead>
<tr>
<th>Substances influencing gastric pH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs, SNRIs</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pantoprazole</strong></td>
</tr>
<tr>
<td><strong>Ranitidine</strong></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.

Paediatric population

Interaction studies have only been performed in adults.

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

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

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate. In total, about 9% of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days), 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 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 adult patients treated for DVT/PE. Furthermore, bleeding occurred in 19.4% of patients in the DVT/PE prevention trial RE-MEDY (adult patients) and in 10.5% of patients in the DVT/PE prevention trial RE-SONATE (adult patients).

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 provided in tables 13-17 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 12 shows the adverse reactions identified from studies and post-marketing data in the indications primary VTE prevention after hip or knee replacement surgery, prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation, DVT/PE treatment and 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 <1/100), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 12: 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>Neutropenia</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</td>
<td>Not known</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>Diagnosis</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>--------</td>
<td>----------</td>
<td>----------</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>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrintestinal ulcer, including oesophageal ulcer</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrooesphagitis</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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
<td></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>Alopecia</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourological haemorrhage, including haematuria</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Bloody discharge</td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic haemorrhage</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Post procedural haematoma</td>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia postoperative</td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post procedural discharge</td>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound secretion</td>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound drainage</td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post procedural drainage</td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of dabigatran etexilate 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 dabigatran etexilate 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 and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. For adult patients, a specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

Primary prevention of VTE in orthopaedic surgery

The table 13 shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the two pivotal clinical trials, according to dose.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 150 mg once daily N (%)</th>
<th>Dabigatran etexilate 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 14 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>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</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 randomised to dabigatran etexilate 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin \( p < 0.05 \). Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomised to 110 mg dabigatran etexilate twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 \( p=0.0027 \)). Subjects randomised to 150 mg dabigatran etexilate 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 dabigatran etexilate therapy.

**Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (DVT/PE treatment)**

Table 15 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of DVT and 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 15: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of DVT and PE**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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 dabigatran etexilate or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events, which occurred during dabigatran etexilate therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Table 16 shows bleeding events in pivotal study RE-MEDY testing prevention of DVT and PE. Some bleeding events (MBEs/CRBEs; any bleeding) were significantly lower at a nominal alpha level of 5% in patients receiving dabigatran etexilate as compared with those receiving warfarin.
Table 16: Bleeding events in study RE-MEDY testing prevention of DVT and PE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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>Intra-cranial 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 /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>

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

Table 17 shows bleeding events in pivotal study RE-SONATE testing prevention of DVT and 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 dabigatran etexilate.

Table 17: Bleeding events in study RE-SONATE testing prevention of DVT and PE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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>Intra-cranial 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 bleed</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

Agranulocytosis and neutropenia

Agranulocytosis and neutropenia have been reported very rarely during post approval use of dabigatran etexilate. Because adverse reactions are reported in the postmarketing surveillance setting from a population of uncertain size, it is not possible to reliably determine their frequency. The reporting rate was estimated as 7 events per 1 million patient years for agranulocytosis and as 5 events per 1 million patient years for neutropenia.
Paediatric population

The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 18 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. 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 18: Adverse reactions

<table>
<thead>
<tr>
<th>SOC / Preferred term.</th>
<th>Frequency</th>
<th>treatment of VTE and prevention of recurrent VTE in paediatric patients</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></td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Gastroesophagitis</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/ Liver function Test abnormal</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourological haemorrhage, including haematuria</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic haemorrhage</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

**Bleeding reactions**

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

**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**

Dabigatran etexilate 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 dabigatran etexilate 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, dabigatran etexilate 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 adult patients in situations when rapid reversal of the anticoagulant effect of dabigatran is required the specific reversal agent (idarucizumab) antagonizing the pharmacodynamic effect of dabigatran is available. The efficacy and safety of idarucizumab have not been established in paediatric patients (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 6) is considered to be associated with an increased risk of bleeding.

**Primary prevention of VTE 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 DVT and 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.

**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 VTE prophylaxis following major joint replacement surgery**

In 2 large randomised, parallel group, double-blind, dose-confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received 75 mg or 110 mg dabigatran etexilate 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 220 mg and 150 mg dabigatran etexilate 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 19). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 19). 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 19.

Data for the total VTE and all cause mortality endpoint are shown in table 20.

Data for adjudicated major bleeding endpoints are shown in table 21 below.

Table 19: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg once daily</th>
<th>Dabigatran etexilate 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 20: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg once daily</th>
<th>Dabigatran etexilate 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 21: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg once daily</th>
<th>Dabigatran etexilate 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 (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multi-national, randomised 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 randomised, with a mean age of 71.5 years and a mean CHADS

score of 2.1. The patient population was 64% male, 70% Caucasian and 16% Asian. For patients randomised 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 22-24 display details of key results in the overall population:

**Table 22: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY.**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</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>
Table 23: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</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. 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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
</tbody>
</table>

% refers to yearly event rate

Table 24: Analysis of all cause and cardiovascular survival during the study period in RE-LY.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<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>
<tr>
<td>p-value</td>
<td>0.1308</td>
<td>0.0517</td>
<td></td>
</tr>
<tr>
<td>Vascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>289 (2.43)</td>
<td>274 (2.28)</td>
<td>317 (2.69)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95% CI)</td>
<td>0.90 (0.77, 1.06)</td>
<td>0.85 (0.72, 0.99)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.2081</td>
<td>0.0430</td>
<td></td>
</tr>
</tbody>
</table>

% refers to yearly event rate

Tables 25-26 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 25: Hazard Ratio and 95 % CI for stroke/systemic embolism by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dabigatran etexilate 110 mg twice daily vs. Warfarin</th>
<th>Dabigatran etexilate 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, 1.21)</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 etexilate and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.

Table 26: Hazard Ratio and 95 % CI for major bleeds by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dabigatran etexilate 110 mg twice daily vs. Warfarin</th>
<th>Dabigatran etexilate 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.
Data from non-interventional studies

A non-interventional study (GLORIA-AF) prospectively collected (in its second phase) safety and effectiveness data in newly diagnosed NVAF patients on dabigatran etexilate in a real-world setting. The study included 4,859 patients on dabigatran etexilate (55% treated with 150 mg bid, 43% treated with 110 mg bid, 2% treated with 75 mg bid). Patients were followed-up for 2 years. The mean CHADS\textsuperscript{2} and HAS-BLED scores were 1.9 and 1.2, respectively. Mean on-therapy follow-up time was 18.3 months. Major bleeding occurred in 0.97 per 100 patient-years. Life-threatening bleeding was reported in 0.46 per 100 patient-years, intracranial haemorrhage in 0.17 per 100 patient-years and gastrointestinal bleeding in 0.60 per 100 patient-years. Stroke occurred in 0.65 per 100 patient-years.

In addition, in a non-interventional study [Graham DJ et al., Circulation. 2015;131:157-164] in more than 134,000 elderly patients with NVAF in the United States (contributing more than 37,500 patient-years of on-therapy follow-up time) dabigatran etexilate (84% patients treated with 150 mg bid, 16% patients treated with 75 mg bid) was associated with a reduced risk of ischemic stroke (hazard ratio 0.80, 95% confidence interval [CI] 0.67 – 0.96), intracranial haemorrhage (hazard ratio 0.34, CI 0.26 – 0.46), and mortality (hazard ratio 0.86, CI 0.77 – 0.96) and increased risk of gastrointestinal bleeding (hazard ratio 1.28, CI 1.14 – 1.44) compared to warfarin. No difference was found for major bleeding (hazard ratio 0.97, CI 0.88 – 1.07).

These observations in real-world settings are consistent with the established safety and efficacy profile for dabigatran etexilate in the RE-LY study in this indication.

Patients who underwent percutaneous coronary intervention (PCI) with stenting

A prospective, randomised, open-label, blinded endpoint (PROBE) study (Phase IIIb) to evaluate dual-therapy with dabigatran etexilate (110 mg or 150 mg bid) plus clopidogrel or ticagrelor (P2Y\textsubscript{12} antagonist) vs. triple-therapy with warfarin (adjusted to a INR 2.0 – 3.0) plus clopidogrel or ticagrelor and ASA was conducted in 2725 patients with non valvular atrial fibrillation who underwent a PCI with stenting (RE-DUAL PCI). Patients were randomised to dabigatran etexilate 110 mg bid dual-therapy, dabigatran etexilate 150 mg bid dual-therapy or warfarin triple-therapy. Elderly patients outside of the United States (≥80 years of age for all countries, ≥70 years of age for Japan) were randomly assigned to the dabigatran etexilate 110 mg dual-therapy group or the warfarin triple-therapy group. The primary endpoint was a combined endpoint of major bleeds based on ISTH definition or clinically relevant non-major bleeding event.

The incidence of the primary endpoint was 15.4% (151 patients) in the dabigatran etexilate 110 mg dual-therapy group as compared with 26.9% (264 patients) in the warfarin triple-therapy group (HR 0.52; 95% CI 0.42, 0.63; P=0.0001 for non-inferiority and P=0.0001 for superiority) and 20.2% (154 patients) in the dabigatran etexilate 150 mg dual-therapy group as compared with 25.7% (196 patients) in the corresponding warfarin triple-therapy group (HR 0.72; 95% CI 0.58, 0.88; P=0.0001 for non-inferiority and P=0.002 for superiority). As part of the descriptive analysis, TIMI (Thrombolysis In Myocardial Infarction) major bleeding events was lower in both dabigatran etexilate dual-therapy groups than in the warfarin triple-therapy group: 14 events (1.4%) in the dabigatran etexilate 110 mg dual-therapy group as compared with 37 events (3.8%) in the warfarin triple-therapy group (HR 0.37; 95% CI 0.20, 0.68; P=0.002) and 16 events (2.1%) in the dabigatran etexilate 150 mg dual-therapy group as compared with 30 events (3.9%) in the corresponding warfarin triple-therapy group (HR 0.51; 95% CI 0.28, 0.93; P=0.03). Both dabigatran etexilate dual-therapy groups had lower rates of intracranial hemorrhage than the corresponding warfarin triple-therapy group: 3 events (0.3%) in the 110 mg dabigatran etexilate dual-therapy group as compared with 10 events (1.0%) in the warfarin triple-therapy group (HR 0.30; 95% CI 0.08, 1.07; P=0.06) and 1 event (0.1%) in the 150 mg dabigatran etexilate dual-therapy group as compared with 8 events (1.0%) in the corresponding warfarin triple-therapy group (HR 0.12; 95% CI 0.02, 0.98; P=0.047). The incidence of the composite efficacy endpoint of death, thromboembolic events (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization in the two dabigatran etexilate dual-therapy groups combined was non-inferior to the warfarin triple-therapy group (13.7% vs. 13.4% respectively; HR 1.04; 95% CI: 0.84, 1.29; P=0.0047 for non-inferiority). There were no statistical differences in the
individual components of the efficacy endpoints between either dabigatran etexilate dual-therapy groups and warfarin triple-therapy.

This study demonstrated that dual-therapy with dabigatran etexilate and a P2Y12 antagonist significantly reduced the risk of bleeding vs. warfarin triple-therapy with non-inferiority for composite of thromboembolic events in patients with atrial fibrillation who underwent a PCI with stenting.

**Treatment of DVT and 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 randomised 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 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 pooled studies RE-COVER and RE-COVER II

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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>
</tbody>
</table>

**Secondary efficacy endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<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 DVT and PE in adults (DVT/PE prevention)**

Two randomised, 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 randomised and 2,856 patients were treated. Duration of dabigatran etexilate treatment ranged from 6 to 36 months (median 534.0 days). For patients randomised 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 28: 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>Dabigatran etexilate 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</td>
<td>1.35</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td>(0.78, 2.64)</td>
<td>(0.57, 2.64)</td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>2.85</td>
<td>2.85</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>0.4</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>2.85</td>
<td>2.85</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 29: 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>Dabigatran etexilate 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

Clinical trials in VTE prophylaxis following major joint replacement surgery

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

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 indication of primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery and the indication of prevention of stroke and systemic embolism in patients with NVAF (see section 4.2 for information on paediatric use).
Treatment of VTE and prevention of recurrent VTE in paediatric patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.

In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.

Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.

Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate arm and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.

Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.
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 characterised 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 30.

**Special populations**

**Renal insufficiency**

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

In a small number of adult 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 30: 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>Mean (gCV %; range)</th>
<th>Half-life [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80</td>
<td>13.4 (25.7%; 11.0-21.6)</td>
<td></td>
</tr>
<tr>
<td>≥50–&lt;80</td>
<td>15.3 (42.7%;11.7-34.1)</td>
<td></td>
</tr>
<tr>
<td>≥30–&lt;50</td>
<td>18.4 (18.5%;13.3-23.0)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>27.2 (15.3%; 21.6-35.0)</td>
<td></td>
</tr>
</tbody>
</table>

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomised 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 adult 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-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 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 adult 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 adult 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 adult 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.

Paediatric population
Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT/PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to <2-year-old, 2 to <12-year-old and 12 to <18-year-old paediatric VTE patients, respectively.

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 a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

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
Hypermellose

Black printing ink
Shellac
Iron oxide black
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

Perforated aluminium unit dose blisters of 10 x 1 hard capsules. Each carton contains 10, 30 or 60 hard capsules.
Multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules). Each individual pack of the multipack contains 6 perforated aluminium unit dose blisters of 10 x 1 hard capsules.
Multipack containing 2 packs of 50 x 1 hard capsules (100 hard capsules). Each individual pack of the multipack contains 5 perforated aluminium unit dose blisters of 10 x 1 hard capsules.
Perforated aluminium unit dose white blisters of 10 x 1 hard capsules. Each carton contains 60 hard capsules.
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 torn 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
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/005
EU/1/08/442/006
EU/1/08/442/007
EU/1/08/442/008
EU/1/08/442/014
EU/1/08/442/015
EU/1/08/442/018
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 18 March 2008
Date of latest renewal: 08 January 2018

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 (approx. 22 x 8 mm) 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

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

4.2 Posology and method of administration

Posology

Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole. Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food. Pradaxa powder and solvent for oral solution should only be used in children aged less than 1 year.

When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

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

Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (DVT/PE)

The recommended doses of dabigatran etexilate 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>Dose recommendation</th>
<th>Dose recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of stroke and systemic embolism in adult patients with NVAF with one or</td>
<td>300 mg dabigatran etexilate taken as one 150 mg capsule</td>
</tr>
<tr>
<td>more risk factors (SPAF)</td>
<td>twice daily</td>
</tr>
<tr>
<td>Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (DVT/PE)</td>
<td>300 mg dabigatran etexilate taken as one 150 mg capsule</td>
</tr>
<tr>
<td></td>
<td>twice daily following treatment with a parenteral</td>
</tr>
<tr>
<td></td>
<td>anticoagulant for at least 5 days</td>
</tr>
<tr>
<td>Dose reduction recommended</td>
<td></td>
</tr>
<tr>
<td>Patients aged ≥80 years</td>
<td>daily dose of 220 mg dabigatran etexilate taken as one</td>
</tr>
<tr>
<td>Patients who receive concomitant verapamil</td>
<td>110 mg capsule twice daily</td>
</tr>
<tr>
<td>Dose reduction for consideration</td>
<td></td>
</tr>
<tr>
<td>Patients with moderate renal impairment (CrCL 30-50 mL/min)</td>
<td>daily dose of dabigatran etexilate of 300 mg or 220 mg</td>
</tr>
<tr>
<td>Patients with gastritis, esophagitis or gastroesophageal reflux</td>
<td>should be selected based on an individual assessment of</td>
</tr>
<tr>
<td></td>
<td>the thromboembolic risk and the risk of bleeding</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 220 mg dabigatran etexilate 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 dabigatran etexilate, 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate 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 dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.

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

**Discontinuation of dabigatran etexilate**

Dabigatran etexilate 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**

Dabigatran etexilate treatment to parenteral anticoagulant:

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

Parenteral anticoagulants to dabigatran etexilate:

The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):

- CrCl $\geq$50 mL/min, VKA should be started 3 days before discontinuing dabigatran etexilate
- CrCl $\geq$30-50 mL/min, VKA should be started 2 days before discontinuing dabigatran etexilate

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

VKA to dabigatran etexilate:

The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is <2.0.

**Cardioversion (SPAF)**

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

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

**Percutaneous coronary intervention (PCI) with stenting (SPAF)**

Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with dabigatran etexilate in combination with antiplatelets after haemostasis is achieved (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 dabigatran etexilate 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 dabigatran etexilate is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran etexilate 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 dabigatran etxelate 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 dabigatran etexilate 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 dabigatran etexilate in the paediatric population for the indication of prevention of stroke and systemic embolism in patients with NVAF.

Treatment of VTE and prevention of recurrent VTE in paediatric patients

For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.

Dabigatran etexilate capsules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate capsules is based on the patient’s weight and age as shown in table 3. The dose should be adjusted according to weight and age as treatment progresses.

For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 3: Single and total daily dabigatran etexilate doses in milligrams (mg) by weight in kilograms (kg) and age in years of the patient

<table>
<thead>
<tr>
<th>Weight /age combinations</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight in kg Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 to &lt;13 8 to &lt;9</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>13 to &lt;16 8 to &lt;11</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>16 to &lt;21 8 to &lt;14</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>21 to &lt;26 8 to &lt;16</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>26 to &lt;31 8 to &lt;18</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>31 to &lt;41 8 to &lt;18</td>
<td>185</td>
<td>370</td>
</tr>
<tr>
<td>41 to &lt;51 8 to &lt;18</td>
<td>220</td>
<td>440</td>
</tr>
<tr>
<td>51 to &lt;61 8 to &lt;18</td>
<td>260</td>
<td>520</td>
</tr>
<tr>
<td>61 to &lt;71 8 to &lt;18</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>71 to &lt;81 8 to &lt;18</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>&gt;81 10 to &lt;18</td>
<td>300</td>
<td>600</td>
</tr>
</tbody>
</table>

Single doses requiring combinations of more than one capsule:

- 300 mg: two 150 mg capsules or four 75 mg capsules
- 260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
- 220 mg: as two 110 mg capsules
- 185 mg: as one 75 mg plus one 110 mg capsule
- 150 mg: as one 150 mg capsule or two 75 mg capsules

Assessment of renal function prior to and during treatment

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).
Treatment with dabigatran etexilate in paediatric patients with eGFR <50 mL/min/1.73m² is contraindicated (see section 4.3).

Patients with an eGFR ≥50 mL/min/1.73m² should be treated with the dose according to table 3.

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

Duration of use

The duration of therapy should be individualised based on the benefit risk assessment.

Missed dose

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. A double dose to make up for missed individual doses must never be taken.

Discontinuation of dabigatran etexilate

Dabigatran etexilate treatment should not be discontinued without medical advice. Patients or their caregivers should be instructed to contact the treating physician if the patient develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

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

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):
Patients should start VKA 3 days before discontinuing dabigatran etexilate. Because dabigatran etexilate can impact the International Normalised Ratio (INR), the INR will better reflect VKA’s effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

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

Method of administration

This medicinal product is for oral use. The capsules can be taken with or without food. The capsules 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
- Severe renal impairment (CrCL <30 mL/min) in adult patients
- eGFR <50 mL/min/1.73m² in paediatric patients
- 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. These are switching anticoagulant therapy (see section 4.2), when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

**Haemorrhagic risk**

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

For adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent idarucizumab is available. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also section 4.9).

In clinical trials, dabigatran etexilate 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: Factors which may increase the haemorrhagic risk.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacodynamic and kinetic factors</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Factors increasing dabigatran plasma levels</strong></td>
<td>Major:</td>
</tr>
<tr>
<td></td>
<td>- Moderate renal impairment in adult patients (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) in adult patients</td>
</tr>
<tr>
<td><strong>Pharmacodynamic interactions (see section 4.5)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ASA and other platelet aggregation inhibitors such as clopidogrel</td>
</tr>
<tr>
<td></td>
<td>- NSAIDs</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><strong>Diseases / procedures with special haemorrhagic risks</strong></td>
<td></td>
</tr>
<tr>
<td></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 adult patients <50 kg (see section 5.2).

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

**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. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected 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 dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5). Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).

Discontinuation of dabigatran etexilate

Patients who develop acute renal failure must discontinue dabigatran etexilate (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 (idarucizumab) may be considered in adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Use of proton-pump inhibitors

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding. In case of paediatric patients local labeling recommendations for proton pump inhibitors have to be followed.

Laboratory coagulation parameters

Although this medicinal product 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.

Dilated 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 dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Table 5 shows coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding. Respective thresholds for paediatric patients are not known (see section 5.1).

Table 5: Coagulation test thresholds at trough for adult patients 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 dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Patients can stay on dabigatran etexilate while being cardioverted. Dabigatran etexilate 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

Dabigatran etexilate should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (idarucizumab) to dabigatran is available for adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

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

Subacute surgery/interventions

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

Elective surgery

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

Table 6 summarises discontinuation rules before invasive or surgical procedures for adult patients.

<table>
<thead>
<tr>
<th>Renal function (CrCL in mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Dabigatran etexilate 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>
Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 7.

**Table 7: Discontinuation rules before invasive or surgical procedures for paediatric patients**

<table>
<thead>
<tr>
<th>Renal function (eGFR in mL/min/1.73m²)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>24 hours before</td>
</tr>
<tr>
<td>50 – 80</td>
<td>2 days before</td>
</tr>
<tr>
<td>&lt;50</td>
<td>These patients have not been studied (see section 4.3).</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 dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

**Postoperative phase**

Dabigatran etexilate treatment should be resumed / started 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 reduced renal function (see also table 4), 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 dabigatran etexilate 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 dabigatran etexilate 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).

**Patients with antiphospholipid syndrome**

Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.
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, paediatric VTE)

The efficacy and safety have not been established for DVT/PE patients with active cancer. There is limited data on efficacy and safety for paediatric patients with active cancer.

Paediatric population

For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

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 8) 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 8: Transporter interactions

<table>
<thead>
<tr>
<th>P-gp inhibitors</th>
<th>Effect on dabigatran concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Increased total dabigatran AUC∞ and Cmax 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∞ and Cmax 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</td>
<td>Based on in vitro results a similar effect as with ketoconazole may be expected.</td>
</tr>
</tbody>
</table>

Concomitant use contraindicated (see section 4.3)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclosporine</strong></td>
<td>The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.</td>
</tr>
<tr>
<td><strong>Glecaprevir / pibrentasvir</strong></td>
<td>Concomitant use not recommended</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>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verapamil</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>When dabigatran etexilate 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><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 3rd day either with or without quinidine. Dabigatran AUC$<em>{\tau,\text{ss}}$ 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><strong>Clarithromycin</strong></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><strong>Ticagrelor</strong></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 $C_{\text{max}}$ 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$<em>{\tau,\text{ss}}$ 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$<em>{\tau,\text{ss}}$ and $C</em>{\text{max,ss}}$ was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran</td>
</tr>
</tbody>
</table>
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$_{ss}$ and C$_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

<table>
<thead>
<tr>
<th>Posaconazole</th>
<th>Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when dabigatran etexilate is co-administered with posaconazole.</th>
</tr>
</thead>
</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 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 dabigatran etexilate.

**P-gp substrate**

**Digoxin**

In a study performed with 24 healthy subjects, when dabigatran etexilate 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 dabigatran etexilate: 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 sulfinpyrazone (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 or during catheter ablation for atrial fibrillation (see section 4.3).

**Table 9: Interactions with anticoagulants and antiplatelet aggregation medicinal products**

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></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&lt;sub&gt;τ,ss&lt;/sub&gt; and C&lt;sub&gt;max,ss&lt;/sub&gt; 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&lt;sub&gt;τ,ss&lt;/sub&gt; and C&lt;sub&gt;max,ss&lt;/sub&gt; were increased by about 30-40% (see section 4.4).</td>
</tr>
<tr>
<td><strong>ASA</strong></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><strong>LMWH</strong></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 10: Other interactions**

<table>
<thead>
<tr>
<th>Substances influencing gastric pH</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</strong></td>
<td>SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups.</td>
</tr>
<tr>
<td><strong>Pantoprazole</strong></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><strong>Ranitidine</strong></td>
<td>Ranitidine administration together with dabigatran etexilate 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.

Paediatric population

Interaction studies have only been performed in adults.

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

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

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate. 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 adult patients treated for DVT/PE. Furthermore, bleeding occurred in 19.4% of patients in the DVT/PE prevention trial RE-MEDY (adult patients) and in 10.5% of patients in the DVT/PE prevention trial RE-SONATE (adult patients).

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 are provided in tables 12-15 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 studies and post-marketing data in the indications prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation, DVT/PE treatment and 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 11: 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>Neutropenia</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</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>Pruritus</td>
<td>Uncommon</td>
<td>Uncommon</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>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>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>
</tbody>
</table>
Abdominal pain | Common | Uncommon
---|---|---
Diarhoea | Common | Uncommon
Dyspepsia | Common | Common
Nausea | Common | Uncommon
Rectal haemorrhage | Uncommon | Common
Haemorrhoidal haemorrhage | Uncommon | Uncommon
Gastrointestinal ulcer, including oesophageal ulcer | Uncommon | Uncommon
Gastroesophagitis | Uncommon | Uncommon
Gastroesophageal reflux disease | Uncommon | Uncommon
Vomiting | Uncommon | Uncommon
Dysphagia | Uncommon | Rare
Hepatobiliary disorders
Hepatic function abnormal/ Liver function Test abnormal | Uncommon | Uncommon
Alanine aminotransferase increased | Uncommon | Uncommon
Aspartate aminotransferase increased | Uncommon | Uncommon
Hepatic enzyme increased | Rare | Uncommon
Hyperbilirubinaemia | Rare | Not known
Skin and subcutaneous tissue disorder
Skin haemorrhage | Common | Common
Alopecia | Not known | Not known
Musculoskeletal and connective tissue disorders
Haemarthrosis | Rare | Uncommon
Renal and urinary disorders
Genitourological haemorrhage, including haematuria | Common | Common
General disorders and administration site conditions
Injection site haemorrhage | Rare | Rare
Catheter site haemorrhage | Rare | Rare
Injury, poisoning and procedural complications
Traumatic haemorrhage | Rare | Uncommon
Incision site haemorrhage | Rare | Rare

**Description of selected adverse reactions**

**Bleeding reactions**

Due to the pharmacological mode of action, the use of dabigatran etexilate 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 dabigatran etexilate 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 and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in
evaluating the condition in any anticoagulated patient. For adult patients, 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 12 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 12: 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>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</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 randomised to dabigatran etexilate 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin [p <0.05]. Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomised to 110 mg dabigatran etexilate twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomised to 150 mg dabigatran etexilate 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 dabigatran etexilate therapy.

Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (DVT/PE treatment)

Table 13 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of DVT and 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 13: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of DVT and PE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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>In 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 dabigatran etexilate or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events, which occurred during dabigatran etexilate therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Table 14 shows bleeding events in pivotal study RE-MEDY testing prevention of DVT and PE. Some bleeding events (MBEs/CRBEs; any bleeding) were significantly lower at a nominal alpha level of 5% in patients receiving dabigatran etexilate as compared with those receiving warfarin.

Table 14: Bleeding events in study RE-MEDY testing prevention of DVT and PE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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>Majority 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/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 bleed</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 15 shows bleeding events in pivotal study RE-SONATE testing prevention of DVT and 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 dabigatran etexilate.
Table 15: Bleeding events in study RE-SONATE testing prevention of DVT and PE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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

Agranulocytosis and neutropenia

Agranulocytosis and neutropenia have been reported very rarely during post approval use of dabigatran etexilate. Because adverse reactions are reported in the postmarketing surveillance setting from a population of uncertain size, it is not possible to reliably determine their frequency. The reporting rate was estimated as 7 events per 1 million patient years for agranulocytosis and as 5 events per 1 million patient years for neutropenia.

Paediatric population

The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 16 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. 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 16: Adverse reactions

<table>
<thead>
<tr>
<th>SOC / Preferred term.</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment of VTE and prevention of recurrent VTE in paediatric patients</td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td>Common/Uncommon</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Common</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Not known</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Common</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>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Common</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td>Not known</td>
</tr>
<tr>
<td>Gastrooesophagitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrooesophageal reflux disease</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/ Liver function Test abnormal</td>
<td>Not known</td>
</tr>
<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>Common</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alopeica</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Genitourological haemorrhage, including haematuria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
</tr>
</tbody>
</table>
Bleeding reactions

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

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

Dabigatran etexilate 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 dabigatran etexilate 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, dabigatran etexilate 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 adult patients in situations when rapid reversal of the anticoagulant effect of dabigatran is required the specific reversal agent (idarucizumab) antagonizing the pharmacodynamic effect of dabigatran is available. The efficacy and safety of idarucizumab have not been established in paediatric patients (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
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.

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 DVT and 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.

*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 (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multi-national, randomised 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 randomised, with a mean age of 71.5 years and a mean CHADS2 score of 2.1. The patient population was 64% male, 70 % Caucasian and 16% Asian. For patients randomised 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 17-19 display details of key results in the overall population:

**Table 17: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY.**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</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 18: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</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>0.3555</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. 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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
</tbody>
</table>

% refers to yearly event rate
Table 19: Analysis of all cause and cardiovascular survival during the study period in RE-LY.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 110 mg twice daily</th>
<th>Dabigatran etexilate 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomised</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<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>
<tr>
<td>p-value</td>
<td>0.1308</td>
<td>0.0517</td>
<td></td>
</tr>
<tr>
<td>Vascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>289 (2.43)</td>
<td>274 (2.28)</td>
<td>317 (2.69)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95 % CI)</td>
<td>0.90 (0.77, 1.06)</td>
<td>0.85 (0.72, 0.99)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.2081</td>
<td>0.0430</td>
<td></td>
</tr>
</tbody>
</table>

% refers to yearly event rate

Tables 20-21 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 20: Hazard Ratio and 95 % CI for stroke/systemic embolism by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dabigatran etexilate 110 mg twice daily vs. warfarin</th>
<th>Dabigatran etexilate 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 etexilate and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.
Table 21: Hazard Ratio and 95% CI for major bleeds by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dabigatran etexilate 110 mg twice daily vs. warfarin</th>
<th>Dabigatran etexilate 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 assigned 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.

Data from non-interventional studies

A non-interventional study (GLORIA-AF) prospectively collected (in its second phase) safety and effectiveness data in newly diagnosed NVAF patients on dabigatran etexilate in a real-world setting. The study included 4,859 patients on dabigatran etexilate (55% treated with 150 mg bid, 43% treated with 110 mg bid, 2% treated with 75 mg bid). Patients were followed-up for 2 years. The mean CHADS2 and HAS-BLED scores were 1.9 and 1.2, respectively. Mean on-therapy follow-up time was 18.3 months. Major bleeding occurred in 0.97 per 100 patient-years. Life-threatening bleeding was reported in 0.46 per 100 patient-years, intracranial haemorrhage in 0.17 per 100 patient-years and gastrointestinal bleeding in 0.60 per 100 patient-years. Stroke occurred in 0.65 per 100 patient-years.

In addition, in a non-interventional study [Graham DJ et al., Circulation. 2015;131:157-164] in more than 134,000 elderly patients with NVAF in the United States (contributing more than 37,500 patient-years of on-therapy follow-up time) dabigatran etexilate (84% patients treated with 150 mg bid, 16% patients treated with 75 mg bid) was associated with a reduced risk of ischemic stroke (hazard ratio 0.80, 95% confidence interval [CI] 0.67 – 0.96), intracranial haemorrhage (hazard ratio 0.34, CI 0.26 – 0.46), and mortality (hazard ratio 0.86, CI 0.77 – 0.96) and increased risk of gastrointestinal bleeding (hazard ratio 1.28, CI 1.14 – 1.44) compared to warfarin. No difference was found for major bleeding (hazard ratio 0.97, CI 0.88 – 1.07).

These observations in real-world settings are consistent with the established safety and efficacy profile for dabigatran etexilate in the RE-LY study in this indication.
Patients undergoing catheter ablation for atrial fibrillation

A prospective, randomised, 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.

Patients who underwent percutaneous coronary intervention (PCI) with stenting

A prospective, randomised, open-label, blinded endpoint (PROBE) study (Phase IIIb) to evaluate dual-therapy with dabigatran etexilate (110 mg or 150 mg bid) plus clopidogrel or ticagrelor (P2Y12 antagonist) vs. triple-therapy with warfarin (adjusted to a INR 2.0 – 3.0) plus clopidogrel or ticagrelor and ASA was conducted in 2725 patients with non valvular atrial fibrillation who underwent a PCI with stenting (RE-DUAL PCI). Patients were randomised to dabigatran etexilate 110 mg bid dual-therapy, dabigatran etexilate 150 mg bid dual-therapy or warfarin triple-therapy. Elderly patients outside of the United States (≥80 years of age for all countries, ≥70 years of age for Japan) were randomly assigned to the dabigatran etexilate 110 mg dual-therapy group or the warfarin triple-therapy group. The primary endpoint was a combined endpoint of major bleeds based on ISTH definition or clinically relevant non-major bleeding event.

The incidence of the primary endpoint was 15.4% (151 patients) in the dabigatran etexilate 110 mg dual-therapy group as compared with 26.9% (264 patients) in the warfarin triple-therapy group (HR 0.52; 95% CI 0.42, 0.63; P<0.0001 for non-inferiority and P=0.0001 for superiority) and 20.2% (154 patients) in the dabigatran etexilate 150 mg dual-therapy group as compared with 25.7% (196 patients) in the corresponding warfarin triple-therapy group (HR 0.72; 95% CI 0.58, 0.88; P<0.0001 for non-inferiority and P=0.002 for superiority). As part of the descriptive analysis, TIMI (Thrombolysis In Myocardial Infarction) major bleeding events was lower in both dabigatran etexilate dual-therapy groups than in the warfarin triple-therapy group: 14 events (1.4%) in the dabigatran etexilate 110 mg dual-therapy group as compared with 37 events (3.8%) in the warfarin triple-therapy group (HR 0.37; 95% CI 0.20, 0.68; P=0.002) and 16 events (2.1%) in the dabigatran etexilate 150 mg dual-therapy group as compared with 30 events (3.9%) in the corresponding warfarin triple-therapy group (HR 0.51; 95% CI 0.28, 0.93; P=0.03). Both dabigatran etexilate dual-therapy groups had lower rates of intracranial hemorrhage than the corresponding warfarin triple-therapy group: 3 events (0.3%) in the 110 mg dabigatran etexilate dual-therapy group as compared with 10 events (1.0%) in the warfarin triple-therapy group (HR 0.30; 95% CI 0.08, 1.07; P=0.06) and 1 event (0.1%) in the 150 mg dabigatran etexilate dual-therapy group as compared with 8 events (1.0%) in the corresponding warfarin triple-therapy group (HR 0.12; 95% CI 0.02, 0.98; P=0.047). The incidence of the composite efficacy endpoint of death, thromboembolic events (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization in the two dabigatran etexilate dual-therapy groups combined was non-inferior to the warfarin triple-therapy group (13.7% vs. 13.4% respectively; HR 1.04; 95% CI: 0.84, 1.29; P=0.0047 for non-inferiority). There were no statistical differences in the individual components of the efficacy endpoints between either dabigatran etexilate dual-therapy groups and warfarin triple-therapy.

This study demonstrated that dual-therapy with dabigatran etexilate and a P2Y12 antagonist significantly reduced the risk of bleeding vs. warfarin triple-therapy with non-inferiority for composite of thromboembolic events in patients with atrial fibrillation who underwent a PCI with stenting.
Treatment of DVT and 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 randomised 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 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 pooled studies RE-COVER and RE-COVER II

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 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</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 DVT and PE in adults (DVT/PE prevention)**

Two randomised, 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 randomised and 2,856 patients were treated. Duration of dabigatran etexilate treatment ranged from 6 to 36 months (median 534.0 days). For patients randomised 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 23: 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>Dabigatran etexilate 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 (95% confidence interval)</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 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 24: 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>Dabigatran etexilate 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

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

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 indication of prevention of stroke and systemic embolism in patients with NVAF (see section 4.2 for information on paediatric use).

Treatment of VTE and prevention of recurrent VTE in paediatric patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.

In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years. Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years. Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate arm and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.

Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start.
Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

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 characterised 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 25.

Special populations

Renal insufficiency

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

In a small number of adult 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 25: 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 randomised 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 adult 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-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 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 Cmax 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 adult 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 adult 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 adult 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 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.

**Paediatric population**
Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT/PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to <2-year-old, 2 to <12-year-old and 12 to <18-year-old paediatric VTE patients, respectively.

**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 a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

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
Hypromellose
Dimeticone 350
Talc
Hydroxypropylcellulose

Capsule shell
Carrageenan
Potassium chloride
Titanium dioxide
Indigo carmine
Hypromellose

Black printing ink
Shellac
Iron oxide black
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

Perforated aluminium unit dose blisters of 10 x 1 hard capsules. Each carton contains 10, 30 or 60 hard capsules. 
Multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules). Each individual pack of the multipack contains 6 perforated aluminium unit dose blisters of 10 x 1 hard capsules. 
Multipack containing 2 packs of 50 x 1 hard capsules (100 hard capsules). Each individual pack of the multipack contains 5 perforated aluminium unit dose blisters of 10 x 1 hard capsules. 
Perforated aluminium unit dose white blisters of 10 x 1 hard capsules. Each carton contains 60 hard capsules. 
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 
55216 Ingelheim am Rhein 
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/009 
EU/1/08/442/010
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2008
Date of latest renewal: 08 January 2018

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 20 mg coated granules
Pradaxa 30 mg coated granules
Pradaxa 40 mg coated granules
Pradaxa 50 mg coated granules
Pradaxa 110 mg coated granules
Pradaxa 150 mg coated granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains coated granules with 20 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 30 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 40 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 50 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 110 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 150 mg dabigatran etexilate (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated granules.

Yellowish coated granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

4.2 Posology and method of administration

Posology

Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food. Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole. Pradaxa powder and solvent for oral solution should only be used in children aged less than 1 year.

When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.
Dabigatran etexilate coated granules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate coated granules is based on the patient’s weight and age as shown in tables 1 and 2. The dose should be adjusted according to weight and age as treatment progresses.

For weight and age combinations not listed in the dosing tables no dosing recommendation can be provided.

**Table 1:** Single and total daily dabigatran etexilate doses in milligrams (mg) for patients aged less than 12 months. The doses depend on weight in kilograms (kg) and age in months of the patient.

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Age in MONTHS</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 to &lt;3</td>
<td>4 to &lt;5</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>3 to &lt;6</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>1 to &lt;3</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;8</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>5 to &lt;7</td>
<td>0 to &lt;1</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>1 to &lt;5</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>5 to &lt;8</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>8 to &lt;12</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>7 to &lt;9</td>
<td>3 to &lt;4</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>4 to &lt;9</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>9 to &lt;12</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>9 to &lt;11</td>
<td>5 to &lt;6</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>6 to &lt;11</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>11 to &lt;12</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>11 to &lt;13</td>
<td>8 to &lt;10</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>10 to &lt;12</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>13 to &lt;16</td>
<td>10 to &lt;11</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>11 to &lt;12</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

20 mg: One 20 mg sachet  
30 mg: One 30 mg sachet  
40 mg: One 40 mg sachet  
50 mg: One 50 mg sachet  
60 mg: Two 30 mg sachets  
70 mg: One 30 mg plus one 40 mg sachet  
80 mg: Two 40 mg sachets  
100 mg: Two 50 mg sachets
Table 2: Single and total daily dabigatran etexilate doses in milligrams (mg) for patients aged 1 year to less than 12 years. The doses depend on weight in kilograms (kg) and age in years of the patient.

<table>
<thead>
<tr>
<th>Weight / age combinations</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight in kg</td>
<td>Age in YEARS</td>
<td></td>
</tr>
<tr>
<td>5 to &lt;7</td>
<td>1 to &lt;2</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;4</td>
<td>70</td>
</tr>
<tr>
<td>7 to &lt;9</td>
<td>1 to &lt;2</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;4</td>
<td>80</td>
</tr>
<tr>
<td>9 to &lt;11</td>
<td>1 to &lt;1.5</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>1.5 to &lt;7</td>
<td>80</td>
</tr>
<tr>
<td>11 to &lt;13</td>
<td>1 to &lt;1.5</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>1.5 to &lt;2.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2.5 to &lt;9</td>
<td>110</td>
</tr>
<tr>
<td>13 to &lt;16</td>
<td>1 to &lt;1.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>1.5 to &lt;2</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;12</td>
<td>140</td>
</tr>
<tr>
<td>16 to &lt;21</td>
<td>1 to &lt;2</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;12</td>
<td>140</td>
</tr>
<tr>
<td>21 to &lt;26</td>
<td>1.5 to &lt;2</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;12</td>
<td>180</td>
</tr>
<tr>
<td>26 to &lt;31</td>
<td>2.5 to &lt;12</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>31 to &lt;41</td>
<td>180</td>
</tr>
<tr>
<td>41 to &lt;51</td>
<td>4 to &lt;12</td>
<td>260</td>
</tr>
<tr>
<td>51 to &lt;61</td>
<td>5 to &lt;12</td>
<td>300</td>
</tr>
<tr>
<td>61 to &lt;71</td>
<td>6 to &lt;12</td>
<td>300</td>
</tr>
<tr>
<td>71 to &lt;81</td>
<td>7 to &lt;12</td>
<td>300</td>
</tr>
<tr>
<td>&gt;81</td>
<td>10 to &lt;12</td>
<td>300</td>
</tr>
</tbody>
</table>

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

- 50 mg: One 50 mg sachet
- 60 mg: Two 30 mg sachets
- 70 mg: One 30 mg plus one 40 mg sachet
- 80 mg: Two 40 mg sachets
- 100 mg: Two 50 mg sachets
- 110 mg: One 110 mg sachet
- 140 mg: One 30 mg plus one 110 mg sachet
- 180 mg: One 30 mg plus one 150 mg sachet
- 220 mg: Two 110 mg sachets
- 260 mg: One 110 mg plus one 150 mg sachet
- 300 mg: Two 150 mg sachets

Assessment of renal function prior to and during treatment

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).

Treatment with dabigatran etexilate in paediatric patients with eGFR <50 mL/min/1.73m² is contraindicated (see section 4.3).

Patients with an eGFR ≥ 50 mL/min/1.73m² should be treated with the dose according to tables 1 and 2.

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

Duration of use

The duration of therapy should be individualised based on the benefit risk assessment.
Missed dose

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. A double dose to make up for missed individual doses must never be taken. If a dose has only been taken partially, there should be no attempt to administer a second dose at that time-point, and the next dose should be taken as scheduled approximately 12 hours later.

Discontinuation of dabigatran etexilate

Dabigatran etexilate treatment should not be discontinued without medical advice. Caregivers should be instructed to contact the treating physician if their treated child develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

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

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):
Patients should start VKA 3 days before discontinuing dabigatran etexilate. Because dabigatran etexilate can impact the international normalised ratio (INR), the INR will better reflect VKA’s effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

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

Method of administration

This medicinal product is for oral use.

The coated granules should be mixed with food prior to intake and only be used with apple juice or the soft foods mentioned in the instructions for use. After mixing with food or apple juice, the medicinal product has to be administered within 30 minutes. The coated granules are not compatible with milk or milk products.

This medicinal product is not compatible with feeding tubes.

Detailed instructions for the use of this medicinal product are provided in ‘Instructions for use’ in the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- eGFR <50 mL/min/1.73m² in paediatric patients
- 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. These are 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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Dabigatran etexilate 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. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

The efficacy and safety of the specific reversal agent idarucizumab used for adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also 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 3 summarises factors which may increase the haemorrhagic risk.

Table 3: Risk factors which may increase the haemorrhagic risk.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Major:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors increasing dabigatran plasma levels</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>Pharmacodynamic interactions (see section 4.5)</td>
<td>ASA and other platelet aggregation inhibitors such as clopidogrel</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>SSRI s 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>

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

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. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected 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 dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5).

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

Patients who develop acute renal failure must discontinue dabigatran etexilate.

When severe bleedings occur, treatment must be discontinued and the source of bleeding investigated. The efficacy and safety of the specific reversal agent (idarucizumab) to dabigatran have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Laboratory coagulation parameters

Although this medicinal product 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 dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Coagulation test thresholds at trough for paediatric patients that may be associated with an increased risk of bleeding are not known.

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

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

Emergency surgery or urgent procedures

Dabigatran etexilate should be temporarily discontinued.

The efficacy and safety of the specific reversal agent (idarucizumab) to dabigatran have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Subacute surgery/interventions

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

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

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 4.

Table 4: Discontinuation rules before invasive or surgical procedures for paediatric patients

<table>
<thead>
<tr>
<th>Renal function (eGFR in mL/min/1.73m²)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>24 hours before</td>
</tr>
<tr>
<td>50 – 80</td>
<td>2 days before</td>
</tr>
<tr>
<td>&lt;50</td>
<td>These patients have not been studied (see section 4.3).</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 dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Postoperative phase

Dabigatran etexilate treatment should be resumed / started 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 (see table 3) 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 dabigatran etexilate 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 dabigatran etexilate 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).

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-
glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

**Active cancer patients**

There is limited data on efficacy and safety for paediatric patients with active cancer.

**Very specific paediatric population**

For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

**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. See also sections 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(<em>{0-\infty}) and (C</em>{\text{max}}) 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(<em>{0-\infty}) and (C</em>{\text{max}}) 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>
<tr>
<td>Glecaprevir / pibrentasvir</td>
<td>The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.</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 section 4.4)**
### 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 section 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 dabigatran etexilate 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 section 4.4).

### Quinidine

When 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$_{\tau,ss}$ and $C_{\text{max,ss}}$ were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see section 4.4).

### Clarithromycin

When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 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$_{\tau,ss}$ 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$_{\tau,ss}$ 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$_{\tau,ss}$ 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 dabigatran etexilate is co-administered with posaconazole.
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

| 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 dabigatran etexilate. |

P-gp substrate

| Digoxin | In a study performed with 24 healthy subjects, when dabigatran etexilate 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 dabigatran etexilate: 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>Medicinal Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>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 a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY), NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin.</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></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(\text{τ,ss}) and C(\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(\text{τ,ss}) and C(\text{max,ss}) were increased by about 30-40% (see section 4.4).</td>
</tr>
<tr>
<td><strong>ASA</strong></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><strong>LMWH</strong></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 7: Other interactions

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Substances influencing gastric pH</strong></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><strong>Ranitidine</strong></td>
<td>Ranitidine administration together with dabigatran etexilate 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate. The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 8 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. 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 8: Adverse reactions

<table>
<thead>
<tr>
<th>SOC / Preferred term</th>
<th>Treatment of VTE and prevention of recurrent VTE in paediatric patients</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Immune system disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Angioedema</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Urticaria</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Gastroesophagitis</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/ Liver function Test abnormal</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td></td>
<td>Not known</td>
</tr>
</tbody>
</table>
Renal and urinary disorders

| Genitourological haemorrhage, including haematuria | Uncommon |

General disorders and administration site conditions

| Injection site haemorrhage | Not known |
| Catheter site haemorrhage | Not known |

Injury, poisoning and procedural complications

| Traumatic haemorrhage | Uncommon |
| Incision site haemorrhage | Not known |

Description of selected adverse reactions

**Bleeding reactions**

Due to the pharmacological mode of action, the use of dabigatran etexilate 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 dabigatran etexilate 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 and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

**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**

Dabigatran etexilate 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 dabigatran etexilate 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, dabigatran etexilate 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.

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.

Clinical efficacy and safety

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.

In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.

Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.

Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate arm and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.
Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

5.2 Pharmacokinetic properties

Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT / PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to <2-year-old, 2 to <12-year-old and 12 to <18-year-old paediatric VTE patients, respectively.

Experience from adults

Absorption

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

After oral administration of Pradaxa in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with \( C_{\text{max}} \) attained within 0.5 and 2.0 hours post administration. A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration 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. Pradaxa coated granules are not compatible with milk or milk products (see section 4.5).

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

Distribution

In adults, 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**

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.

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 9.

**Special populations**

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

In a small number of adult 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 4.3 and 4.4).

**Table 9: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function (adults).**

<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 randomised pharmacokinetic study in non-valvular atrial fibrillation (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.

**Hepatic impairment**

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

**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 a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

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

Tartaric acid
Acacia
Hypromellose
Dimeticone 350
Talc
Hydroxypropylcellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening of the aluminium bag

Once the aluminium bag containing the sachets with the coated granules and the desiccant is opened, the medicinal product must be used within 6 months.

After first opening of the sachet

The opened sachet cannot be stored and must be used immediately after opening.

After preparation

After mixing with soft food or apple juice, the medicinal product has to be administered within 30 minutes.

6.4 Special precautions for storage

The aluminium bag containing the sachets with the coated granules should only be opened immediately prior to use of the first sachet in order to protect from moisture.

After opening of the aluminium bag, the individual sachets should be kept unopened until immediately prior to use in order to protect from moisture.

6.5 Nature and contents of container

Aluminium bag containing 60 silver-coloured PET/Alu/LDPE sachets with the coated granules and one desiccant (labelled “DO NOT EAT” including pictogram and “SILICA GEL”).

6.6 Special precautions for disposal and other handling

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
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/025
EU/1/08/442/026
EU/1/08/442/027
EU/1/08/442/028
EU/1/08/442/029
EU/1/08/442/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2008
Date of latest renewal: 08 January 2018

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 6.25 mg/mL powder and solvent for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each mL of reconstituted oral solution contains 6.25 mg of dabigatran etexilate (as mesilate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder and solvent for oral solution
Components for reconstitution of the oral solution:
The powder for oral solution is yellowish-white.
The solvent is a clear, colourless solution.
The sucralose powder is white to almost white.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.
For age appropriate dose forms, see section 4.2.
Pradaxa powder and solvent for oral solution should not be used in patients aged 1 year or older.

4.2 Posology and method of administration
Posology
Pradaxa powder and solvent for oral solution should only be used in children aged less than 1 year. Pradaxa coated granules can be used in children aged less than 12 years as soon as the child is able to swallow soft food. Pradaxa capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole.
When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.
For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.

Dabigatran etexilate oral solution should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.
The recommended dose of dabigatran etexilate oral solution is based on the patient’s weight and age as shown in table 1. The dose should be adjusted according to weight and age as treatment progresses.
For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 1: Single and total daily dabigatran etexilate doses in millilitres (mL) by weight in kilograms (kg) and age in months of the patient

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Age in months</th>
<th>Single dose in mL</th>
<th>Total daily dose in mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 to &lt;3</td>
<td>&lt;1 to &lt;4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4 to &lt;5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>&lt;1 to &lt;2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>&lt;1</td>
<td>2</td>
<td>4</td>
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<tr>
<td></td>
<td>1 to &lt;3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>8 to &lt;10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>5 to &lt;7</td>
<td>&lt;1 to &lt;2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>4 to &lt;8</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>8 to &lt;11</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>11 to &lt;12</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>7 to &lt;9</td>
<td>3 to &lt;4</td>
<td>5</td>
<td>10</td>
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<tr>
<td></td>
<td>4 to &lt;6</td>
<td>6</td>
<td>12</td>
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<td>6 to &lt;10</td>
<td>7</td>
<td>14</td>
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<td></td>
<td>10 to &lt;12</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>9 to &lt;11</td>
<td>5 to &lt;7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>7 to &lt;9</td>
<td>8</td>
<td>16</td>
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<td></td>
<td>9 to &lt;12</td>
<td>9</td>
<td>18</td>
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<td>11 to &lt;13</td>
<td>8 to &lt;11</td>
<td>10</td>
<td>20</td>
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<tr>
<td></td>
<td>11 to &lt;12</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>13 to &lt;16</td>
<td>10 to &lt;12</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral solution [mL]</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains dabigatran etexilate [mg]</td>
<td>12.50</td>
<td>18.75</td>
<td>25.00</td>
<td>31.25</td>
<td>37.50</td>
<td>43.75</td>
<td>50.00</td>
<td>56.25</td>
<td>62.50</td>
<td>68.75</td>
<td>75.00</td>
</tr>
</tbody>
</table>

The maximum dose stated in the dosing table for Pradaxa oral solution must not be exceeded (see also section 5.3).

Assessment of renal function prior to and during treatment

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).

Treatment with dabigatran etexilate in paediatric patients with eGFR <50 mL/min/1.73m² is contraindicated (see section 4.3).

Patients with an eGFR ≥ 50 mL/min/1.73m² should be treated with the dose according to table 1.

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

The duration of therapy should be individualised based on the benefit risk assessment.

**Missed dose**

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted. A double dose to make up for missed individual doses must never be taken. If a dose has only been taken partially, there should be no attempt to administer a second dose at that time-point, and the next dose should be taken as scheduled approximately 12 hours later.

**Discontinuation of dabigatran etexilate**

Dabigatran etexilate treatment should not be discontinued without medical advice. Caregivers should be instructed to contact the treating physician if their treated child develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

**Switching**

Dabigatran etexilate treatment to parenteral anticoagulant:

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

Parenteral anticoagulants to dabigatran etexilate:

The parenteral anticoagulant should be discontinued and dabigatran etexilate 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).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):

Patients should start VKA 3 days before discontinuing dabigatran etexilate. Because dabigatran etexilate can impact the international normalised ratio (INR), the INR will better reflect VKA’s effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to dabigatran etexilate:

The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is <2.0.

**Method of administration**

This medicinal product is for oral use.

Instructions For Use must be carefully followed. Detailed instructions for the preparation of the oral solution and the administration with the dosing pipette are provided in ‘Instructions for use’ in the package leaflet.

Pradaxa oral solution should be reconstituted by a healthcare professional. Caregivers may reconstitute the oral solution themselves if the treating physician determines that it is appropriate.

In case the anticoagulant treatment has been initiated in the hospital and has to be continued after discharge the following options are possible:

- the treatment is continued with Pradaxa powder and solvent for oral solution if reconstitution of the oral solution on a daily basis, either by a healthcare professional or a caregiver, is assured. The instructions for use and particularly the storage conditions for the reconstituted oral solution have to always be carefully followed.
- the treatment is continued with Pradaxa coated granules
• the treatment is continued with standard of care

After reconstitution, Pradaxa oral solution is a clear colourless to clear yellowish solution. The pH of the reconstituted oral solution is approximately 2.1.

The oral solution should not be mixed with milk, other beverages or food.

The dosing pipettes provided are not compatible with feeding tubes. The oral solution should not be administered via feeding tubes.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
• eGFR <50 mL/min/1.73m² in paediatric patients
• 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. These are 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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
• Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Dabigatran etexilate 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. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

The efficacy and safety of the specific reversal agent idarucizumab used for adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also 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: Risk factors which may increase the haemorrhagic risk.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors increasing dabigatran plasma levels</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>Pharmacodynamic interactions (see section 4.5)</td>
<td>ASA and other platelet aggregation inhibitors such as clopidogrel</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</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>

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

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. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected 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 dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5). Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).
Discontinuation of dabigatran etexilate

Patients who develop acute renal failure must discontinue dabigatran etexilate.

When severe bleedings occur, treatment must be discontinued and the source of bleeding investigated. The efficacy and safety of the specific reversal agent (idarucizumab) to dabigatran have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Laboratory coagulation parameters

Although this medicinal product 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 dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Coagulation test thresholds at trough for paediatric patients that may be associated with an increased risk of bleeding are not known.

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

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

Emergency surgery or urgent procedures

Dabigatran etexilate should be temporarily discontinued.

The efficacy and safety of the specific reversal agent (idarucizumab) to dabigatran have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Subacute surgery/interventions

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

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

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 3.

**Table 3: Discontinuation rules before invasive or surgical procedures for paediatric patients**

<table>
<thead>
<tr>
<th>Renal function (eGFR in mL/min/1.73m²)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>24 hours before</td>
</tr>
<tr>
<td>50 – 80</td>
<td>2 days before</td>
</tr>
<tr>
<td>&lt;50</td>
<td>These patients have not been studied (see section 4.3).</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 dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Postoperative phase

Dabigatran etexilate treatment should be resumed / started 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 (see table 2) 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 dabigatran etexilate 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 dabigatran etexilate 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).

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-
glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Active cancer patients

There is limited data on efficacy and safety for paediatric patients with active cancer.

Very specific paediatric population

For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 4) 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. See also sections 4.3, 4.4 and 5.1).

Table 4: Transporter interactions

<table>
<thead>
<tr>
<th>P-gp inhibitors</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concomitant use contraindicated (see section 4.3)</strong></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Ketoconazole increased total dabigatran AUC_{0-\infty} and C_{\text{max}} 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_{0-\infty} and C_{\text{max}} 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>
<tr>
<td>Glecaprevir / pibrentasvir</td>
<td>The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.</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 iraconazole 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 section 4.4)**
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verapamil</strong></td>
<td>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 section 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.</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>When dabigatran etexilate 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 section 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 3rd day either with or without quinidine. Dabigatran AUC_{\tau,ss} and C_{\text{max,ss}} were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see section 4.4).</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></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><strong>Ticagrelor</strong></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\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_{\tau,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_{\tau,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_{\tau,ss} and C_{\text{max,ss}} 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.</td>
</tr>
<tr>
<td><strong>Posaconazole</strong></td>
<td>Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when dabigatran etexilate 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

| 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 dabigatran etexilate. |

P-gp substrate

| Digoxin | In a study performed with 24 healthy subjects, when dabigatran etexilate 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 dabigatran etexilale: 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 sulfinpyrazone (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 5: Interactions with anticoagulants and antiplatelet aggregation medicinal products

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>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 a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY), NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin.</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></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&lt;sub&gt;τ,ss&lt;/sub&gt; and C&lt;sub&gt;max,ss&lt;/sub&gt; 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&lt;sub&gt;τ,ss&lt;/sub&gt; and C&lt;sub&gt;max,ss&lt;/sub&gt; were increased by about 30-40% (see section 4.4).</td>
</tr>
<tr>
<td><strong>ASA</strong></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><strong>LMWH</strong></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 6: Other interactions

<table>
<thead>
<tr>
<th>Medicinal Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Substances influencing gastric pH</strong></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><strong>Ranitidine</strong></td>
<td>Ranitidine administration together with dabigatran etexilate 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

Pradaxa powder and solvent for oral solution is intended to be used in children below the age of 12 months. Information regarding pregnancy and breast-feeding will not be relevant in the context of this patient group.

4.7 Effects on ability to drive and use machines

Dabigatran etexilate powder and solvent for oral solution is intended to be used in children below the age of 12 months. Information in this section will not be relevant in the context of this patient group.

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate. The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 7 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. 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 7: 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>treatment of VTE and prevention of recurrent VTE in paediatric patients</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Common</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Not known</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Common</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Common</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td>Not known</td>
</tr>
<tr>
<td>Gastroesophagitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/ Liver function Test abnormal</td>
<td>Not known</td>
</tr>
<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>Common</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Genitourological haemorrhage, including haematuria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Not known</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
</tr>
<tr>
<td>Traumatic haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Not known</td>
</tr>
</tbody>
</table>
Description of selected adverse reactions

**Bleeding reactions**

Due to the pharmacological mode of action, the use of dabigatran etexilate 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 dabigatran etexilate 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 and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

**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

Dabigatran etexilate 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 dabigatran etexilate 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, dabigatran etexilate 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.
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.
Clinical efficacy and safety

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.

In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.

Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.

Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate arm and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.

Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.
5.2 Pharmacokinetic properties

Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT / PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to <2-year-old, 2 to <12-year-old and 12 to <18-year-old paediatric VTE patients, respectively.

Experience from adults

Absorption

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

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

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration 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. Pradaxa oral solution should not be mixed with milk, other beverages or food (see section 4.5).

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

Distribution

In adults, 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

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.

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 8.

Special populations

Renal insufficiency

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

In a small number of adult 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 4.3 and 4.4).

Table 8: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function (adults).

<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 randomised pharmacokinetic study in non-valvular atrial fibrillation (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.

Hepatic impairment

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

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 a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

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. At doses exceeding the maximum recommended human dose for patients aged less than 1 year, a mesilate ester assumed to be mutagenic due to its structure may be present above acceptable levels.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pradaxa powder for oral solution
Mannitol
Hydroxypropylcellulose

Solvent for Pradaxa oral solution
Tartaric acid
Hydrochloric acid (for pH-adjustment)
Water, purified
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening of the aluminium bag

Once the aluminium bag containing the sachets with the powder for oral solution and the desiccant is opened, the medicinal product must be used within 4 months.

After first opening of the sachet with the powder for oral solution

The opened sachet cannot be stored and must be used immediately after opening.

After reconstitution

Once reconstituted, the oral solution in the bottle can be stored for 2 hours below 25°C, or for 18 hours at 2-8°C (refrigerator). The bottles must be stored in an upright position.

6.4 Special precautions for storage

This medicinal product should be stored so that the bottle inside each individual preparation pack is upright.

The aluminium bag containing the sachets with the powder for oral solution should only be opened immediately prior to use of the first sachet in order to protect from moisture.

After opening of the aluminium bag, the individual sachets should be kept unopened until immediately prior to use in order to protect from moisture.

For storage conditions after reconstitution and first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pradaxa powder and solvent for oral solution is supplied as several components for reconstitution in a kit that contains:

- 1 carton box containing the Pradaxa powder for oral solution.
  30 PET/Alu/LDPE sachets are packaged in one aluminium bag that also contains a desiccant (labelled with “DO NOT EAT” including pictogram and “SILICA GEL”). Each sachet contains 180.4 mg powder for oral solution.
- 30 carton boxes which are referred to as individual preparation packs.
  Each pack contains one white PET/Alu/LDPE sachet with 70 mg sucralose powder, one amber glass bottle with a PP/HDPE screw-cap containing 28 mL solvent to prepare the oral solution, two dosing pipettes (12 mL) and one adapter for the bottle.

The co-packaged dosing pipettes and the adapter are medical devices.
On the 12 mL dosing pipette, a scale from 0 to 12 mL with 0.25 mL graduation is printed.
6.6 Special precautions for disposal and other handling

Detailed instructions for the preparation of the oral solution and the administration with the dosing pipette are provided in ‘Instructions for use’ in the package leaflet.

After reconstitution, the oral solution is a clear colourless to clear yellowish solution.

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
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2008
Date of latest renewal: 08 January 2018

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 AUTHORIZATION

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 of Pradaxa capsules:

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

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France

Name and address of the manufacturer(s) responsible for batch release of Pradaxa coated granules:

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

Name and address of the manufacturer(s) responsible for batch release of Pradaxa powder and solvent for oral solution:

Catalent Germany Schorndorf GmbH
Steinbeisstr. 1 und 2
73614 Schorndorf
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 (PSURs)

The requirements for submission of PSURs 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 marketing authorisation holder (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 Guides
- Patient Alert Cards
- A mandatory training video for Pradaxa powder and solvent for oral solution
- Ad hoc technical support via phone for Pradaxa powder and solvent for oral solution

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
- Dosing tables for the different dosage forms (only for paediatric VTE)
- Recommendation for kidney function measurement
- Recommendations for dose reduction in at risk populations (only for adult indications)
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients/carers 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 the patient is 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
- Recommendation that all parents/caregivers of paediatric patients administered Pradaxa powder and solvent for oral solution should be counselled about the reconstitution and dosing of the oral solution

The MAH shall also provide a patient alert card in each pack of the medicinal product, the text of which is included in Annex III.
A digital training video for reconstitution and dosing of the oral solution should contain the following key messages:

- Reconstitution of the oral solution
- Administration of the prepared oral solution and correct use of the devices
- Storage and disposal of the prepared oral solution
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
hard capsule
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
    55216 Ingelheim am Rhein
    Germany

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

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

13. **BATCH NUMBER**

    Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

    Pradaxa 75 mg capsules

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

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

PC
SN
NN
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTER FOR 75 mg

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pradaxa 75 mg hard capsules dabigatran etexilate</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Boehringer Ingelheim (logo)</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peel back</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON WHITE BLISTERS OR STRIPS</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>BLISTER FOR 75 mg</td>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Pradaxa 75 mg hard capsules
dabigatran etexilate

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

   Boehringer Ingelheim (logo)

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**

   Peel back
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
hard capsule
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 medicine 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  
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 capsules (only applicable for folding box, not applicable for bottle label)

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

2D barcode carrying the unique identifier included. (only applicable for folding box, not applicable for bottle label)

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

(only applicable for folding box, not applicable for bottle label)

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

**FOLDING BOX FOR BLISTER for 110 mg**

1. **NAME OF THE MEDICINAL PRODUCT**

Pradaxa 110 mg hard capsules
dabigatran etexilate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

   hard capsule
   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
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

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

<table>
<thead>
<tr>
<th>PC</th>
<th>SN</th>
<th>NN</th>
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<tbody>
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</table>
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
hard capsule
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 AUTHORITY**

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

12. **MARKETING AUTHORITY 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 capsules

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

hard capsule
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
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 capsules

17. UNIQUE IDENTIFIER – 2D BARCODE
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
PC
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NN
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<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>MULTIPACK OF 100 (2 PACKS OF 50 HARD-CAPSULES) – WITHOUT BLUE BOX – 110 mg HARD CAPSULES</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>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
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<tbody>
<tr>
<td>hard capsule</td>
</tr>
<tr>
<td>50x1 hard capsules. Component of a multipack, can’t be sold separately.</td>
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<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>1</th>
<th>Tear-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Peel-off</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>
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<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tbody>
<tr>
<td>8. <strong>EXPIRY DATE</strong></td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>9. <strong>SPECIAL STORAGE CONDITIONS</strong></td>
</tr>
<tr>
<td>10. <strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
</tbody>
</table>
| 11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER** | Boehringer Ingelheim International GmbH  
Binger Str. 173  
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 capsules |
| 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

hard capsule
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
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 capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
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NN
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<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tbody>
<tr>
<td><strong>BLISTER FOR 110 mg</strong></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>Boehringer Ingelheim (logo)</td>
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<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
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<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>
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<tr>
<th>5. OTHER</th>
</tr>
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<tbody>
<tr>
<td>👕 Peel back</td>
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</tbody>
</table>
## MINIMUM PARTICULARS TO APPEAR ON WHITE BLISTERS OR STRIPS

### BLISTER FOR 110 mg

<p>| | |</p>
<table>
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<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
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</tbody>
</table>
|   | 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 |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING.
FOLDING BOX AND LABEL FOR BOTTLE for 110 mg

1. NAME OF THE MEDICINAL PRODUCT
Pradaxa 110 mg hard capsules
dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each hard capsule contains 110 mg dabigatran etexilate (as mesilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
hard capsule
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 medicine 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
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

16. INFORMATION IN BRAILLE
Pradaxa 110 mg capsules (only applicable for folding box, not applicable for bottle label)

17. UNIQUE IDENTIFIER – 2D BARCODE
2D barcode carrying the unique identifier included. (only applicable for folding box, not applicable for bottle label)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
(only applicable for folding box, not applicable for bottle label)
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
- hard capsule
  - 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
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/009 10 x 1 hard capsules
EU/1/08/442/010 30 x 1 hard capsules
EU/1/08/442/011 60 x 1 hard capsules
EU/1/08/442/019 60 x 1 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Pradaxa 150 mg capsules

16. INFORMATION IN BRAILLE

Pradaxa 150 mg capsules

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

hard capsule
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.

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
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 capsules

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

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>Pradaxa 150 mg hard capsules</td>
</tr>
<tr>
<td>dabigatran etexilate</td>
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</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>
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</tbody>
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<table>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>hard capsule</td>
</tr>
<tr>
<td>Multipack: 180 (3 packs of 60x1) hard capsules.</td>
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</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Swallow whole, do not chew or break the capsule.</td>
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<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
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<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<th>8. EXPIRY DATE</th>
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<td>EXP</td>
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<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
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 capsules

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
hard capsule
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
<table>
<thead>
<tr>
<th>Section</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. EXPIRY DATE</td>
<td>EXP</td>
</tr>
<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
<td>Store in the original package in order to protect from moisture.</td>
</tr>
<tr>
<td>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR</td>
<td>OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
<td>Boehringer Ingelheim International GmbH</td>
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<td>Binger Str. 173</td>
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<td>55216 Ingelheim am Rhein</td>
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<td></td>
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<td>12. MARKETING AUTHORISATION NUMBER(S)</td>
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<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
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<tr>
<td>15. INSTRUCTIONS ON USE</td>
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<tr>
<td>16. INFORMATION IN BRAILLE</td>
<td>Pradaxa 150 mg capsules</td>
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</tr>
<tr>
<td>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</td>
<td></td>
</tr>
<tr>
<td><strong>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>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</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
</table>
| Pradaxa 150 mg hard capsules  
dabigatran etexilate |

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

<table>
<thead>
<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
</tr>
</thead>
</table>

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

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

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

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

<table>
<thead>
<tr>
<th><strong>8. EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>9. SPECIAL STORAGE CONDITIONS</strong></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
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 capsules

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><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER FOR 150 mg</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></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><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer Ingelheim (logo)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th><strong>5. OTHER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peel back</td>
</tr>
</tbody>
</table>
### MINIMUM PARTICULARS TO APPEAR ON WHITE BLISTERS OR STRIPS

**BLISTER FOR 150 mg**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **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 |

![Peel back icon]
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

hard capsule
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 medicine 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 |
| | 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 capsules (only applicable for folding box, not applicable for bottle label) |
| 17. | UNIQUE IDENTIFIER – 2D BARCODE |
| | 2D barcode carrying the unique identifier included. (only applicable for folding box, not applicable for bottle label) |
| 18. | UNIQUE IDENTIFIER - HUMAN READABLE DATA |
| | (only applicable for folding box, not applicable for bottle label) |
| | PC |
| | SN |
| | NN |
### 1. NAME OF THE MEDICINAL PRODUCT

- Pradaxa 20 mg coated granules
- Pradaxa 30 mg coated granules
- Pradaxa 40 mg coated granules
- Pradaxa 50 mg coated granules
- Pradaxa 110 mg coated granules
- Pradaxa 150 mg coated granules
- dabigatran etexilate

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains coated granules with 20 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 30 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 40 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 50 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 110 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 150 mg dabigatran etexilate (as mesilate).

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

- coated granules
  - 60 sachets with coated granules

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

- Read the package leaflet before use.
- Oral use
- Patient alert card and package leaflet in local language 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 medicine must be used within 6 months. 
Keep the sachets closed until use. 
After mixing with soft food or apple juice, use within 30 minutes.

9. SPECIAL STORAGE CONDITIONS

The aluminium bag containing the sachets with the Pradaxa coated granules should only be opened immediately prior to use of the first sachet 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 
55216 Ingelheim am Rhein 
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/025 60 x Pradaxa 20 mg coated granules 
EU/1/08/442/026 60 x Pradaxa 30 mg coated granules
EU/1/08/442/027 60 x Pradaxa 40 mg coated granules
EU/1/08/442/028 60 x Pradaxa 50 mg coated granules
EU/1/08/442/029 60 x Pradaxa 110 mg coated granules
EU/1/08/442/030 60 x Pradaxa 150 mg coated granules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE
16. INFORMATION IN BRAILLE

Pradaxa 20 mg coated granules
Pradaxa 30 mg coated granules
Pradaxa 40 mg coated granules
Pradaxa 50 mg coated granules
Pradaxa 110 mg coated granules
Pradaxa 150 mg coated granules

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 INTERMEDIATE PACKAGING
ALUMINIUM BAG FOR COATED GRANULES

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 20 mg coated granules
Pradaxa 30 mg coated granules
Pradaxa 40 mg coated granules
Pradaxa 50 mg coated granules
Pradaxa 110 mg coated granules
Pradaxa 150 mg coated granules
dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains coated granules with 20 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 30 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 40 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 50 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 110 mg dabigatran etexilate (as mesilate).
Each sachet contains coated granules with 150 mg dabigatran etexilate (as mesilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

coated granules
60 sachets with coated granules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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
Once opened, the medicine must be used within 6 months.
Keep the sachets closed until use.
After mixing with soft food or apple juice, use within 30 minutes.

9. SPECIAL STORAGE CONDITIONS

The aluminium bag containing the sachets with the Pradaxa coated granules should only be opened immediately prior to use of the first sachet 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
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/025 60 x Pradaxa 20 mg coated granules
EU/1/08/442/026 60 x Pradaxa 30 mg coated granules
EU/1/08/442/027 60 x Pradaxa 40 mg coated granules
EU/1/08/442/028 60 x Pradaxa 50 mg coated granules
EU/1/08/442/029 60 x Pradaxa 110 mg coated granules
EU/1/08/442/030 60 x Pradaxa 150 mg coated granules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
| SACHET FOR COATED GRANULES |

1. **NAME OF THE MEDICINAL PRODUCT**

   - Pradaxa 20 mg coated granules
   - Pradaxa 30 mg coated granules
   - Pradaxa 40 mg coated granules
   - Pradaxa 50 mg coated granules
   - Pradaxa 110 mg coated granules
   - Pradaxa 150 mg coated granules
   - dabigatran etexilate

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

   - Boehringer Ingelheim (logo)

3. **EXPIRY DATE**

   - EXP

4. **BATCH NUMBER**

   - Lot

5. **OTHER**
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

OUTER BOX – 30 PREPARATIONS – INCLUDING THE BLUE BOX – POWDER AND SOLVENT FOR ORAL SOLUTION

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa 6.25 mg/mL powder and solvent for oral solution</td>
</tr>
<tr>
<td>Medicine kit dabigatran etexilate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each mL of reconstituted oral solution contains 6.25 mg of 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>powder and solvent for oral solution</td>
</tr>
</tbody>
</table>

Pradaxa powder and solvent for oral solution is supplied as several components for reconstitution in a kit that contains:
- 1 carton box containing the Pradaxa powder for oral solution:
  30 aluminium sachets are packaged in one aluminium bag that also contains a desiccant (labelled with “DO NOT EAT” including pictogram and “SILICA GEL”).
- 30 carton boxes which are referred to as individual preparation packs containing:
  One sucralose sachet (70 mg).
  One bottle with solvent (28 mL).
  One pipette adapter for the bottle.
  Two 12 mL dosing pipettes.

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Patient alert card and package leaflet in local language inside.</td>
</tr>
</tbody>
</table>

A training video is available by scanning the QR code.
The same information is also available on the following URL: www.Pradaxa-kids.com
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 the aluminium bag containing the sachets with the Pradaxa powder for oral solution and the desiccant is opened, the medicine must be used within 4 months. Keep the sachets closed until use.

Once prepared, the oral solution in the bottle can be stored for 2 hours below 25°C, or for 18 hours at 2-8°C (refrigerator).

9. SPECIAL STORAGE CONDITIONS

Store upright pictogram for upright storage to be included

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
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
Pradaxa powder and solvent for oral solution

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 INTERMEDIATE PACKAGING
### INNER BOX – INDIVIDUAL PREPARATION PACK FOR ORAL SOLUTION – WITHOUT BLUE BOX

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa 6.25 mg/mL powder and solvent for oral solution</td>
</tr>
<tr>
<td>Individual preparation pack</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each mL of reconstituted oral solution contains 6.25 mg of 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>powder and solvent for oral solution</td>
</tr>
<tr>
<td>Each individual preparation pack contains:</td>
</tr>
<tr>
<td>- One sucralose sachet (70 mg).</td>
</tr>
<tr>
<td>- One bottle with solvent (28 mL).</td>
</tr>
<tr>
<td>- One pipette adapter for the bottle.</td>
</tr>
<tr>
<td>- Two 12 mL dosing pipettes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use</td>
</tr>
</tbody>
</table>

A training video is available by scanning the QR code:
The same information is also available on the following URL: www.Pradaxa-kids.com

<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>
8. **EXPIRY DATE**

EXP

Once prepared, the oral solution in the bottle can be stored for 2 hours below 25°C, or for 18 hours at 2-8°C (refrigerator).

9. **SPECIAL STORAGE CONDITIONS**

Store upright pictogram for upright storage to be included

The bottles must be stored in an upright position.

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
55216 Ingelheim am Rhein
Germany

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

EU/1/08/442/031

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

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

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>INNER BOX – PRADAXA POWDER FOR ORAL SOLUTION – WITHOUT BLUE BOX</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Pradaxa powder for oral solution
dabigatran etexilate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each mL of reconstituted oral solution contains 6.25 mg of dabigatran etexilate (as mesilate).

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

   powder for oral solution

   Contains 30 sachets with Pradaxa powder for oral solution and one desiccant (labelled “DO NOT EAT” including pictogram and “SILICA GEL”) packaged in an aluminium bag.

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

   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

   Once the aluminium bag containing the sachets with the Pradaxa powder for oral solution and the desiccant is opened, the medicine must be used within 4 months. Keep the sachets closed until use.

9. **SPECIAL STORAGE CONDITIONS**

   This medicine does not require any special storage conditions.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10.</strong></td>
<td><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
<tr>
<td><strong>11.</strong></td>
<td><strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td></td>
<td>Boehringer Ingelheim International GmbH</td>
</tr>
<tr>
<td></td>
<td>Binger Str. 173</td>
</tr>
<tr>
<td></td>
<td>55216 Ingelheim am Rhein</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
</tr>
<tr>
<td><strong>12.</strong></td>
<td><strong>MARKETING AUTHORISATION NUMBER(S)</strong></td>
</tr>
<tr>
<td></td>
<td>EU/1/08/442/031</td>
</tr>
<tr>
<td><strong>13.</strong></td>
<td><strong>BATCH NUMBER</strong></td>
</tr>
<tr>
<td></td>
<td>Lot</td>
</tr>
<tr>
<td><strong>14.</strong></td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong></td>
</tr>
<tr>
<td><strong>15.</strong></td>
<td><strong>INSTRUCTIONS ON USE</strong></td>
</tr>
<tr>
<td><strong>16.</strong></td>
<td><strong>INFORMATION IN BRAILLE</strong></td>
</tr>
<tr>
<td><strong>17.</strong></td>
<td><strong>UNIQUE IDENTIFIER – 2D BARCODE</strong></td>
</tr>
<tr>
<td><strong>18.</strong></td>
<td><strong>UNIQUE IDENTIFIER – HUMAN READABLE DATA</strong></td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>ALUMINIUM BAG – PRADAXA POWDER FOR ORAL SOLUTION</td>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Pradaxa powder for oral solution
dabigatran etexilate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

powder for oral solution

30 sachets with 180.4 mg Pradaxa powder for oral solution
1 desiccant (labelled with “DO NOT EAT” including pictogram and “SILICA GEL”)

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

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

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

8. **EXPIRY DATE**

EXP

Once the aluminium bag containing the sachets with the Pradaxa powder for oral solution and the desiccant is opened, the medicine must be used within 4 months. Keep the sachets closed until use.

9. **SPECIAL STORAGE CONDITIONS**

This medicine does not require any special storage conditions.
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 AUTHORIZATION HOLDER

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

12. MARKETING AUTHORIZATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING SOLVENT BOTTLE LABEL FOR ORAL SOLUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Solvent for Pradaxa 6.25 mg/mL oral solution</td>
</tr>
<tr>
<td><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
</tr>
<tr>
<td>Each bottle contains 28 mL of solvent.</td>
</tr>
<tr>
<td><strong>3. LIST OF EXCIPIENTS</strong></td>
</tr>
<tr>
<td><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></td>
</tr>
<tr>
<td>solvent for oral solution</td>
</tr>
<tr>
<td><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</strong></td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
<tr>
<td><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></td>
</tr>
<tr>
<td><strong>8. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>Once prepared, the oral solution in the bottle can be stored for 2 hours below 25°C, or for 18 hours at 2-8°C (refrigerator). The bottles must be stored in an upright position.</td>
</tr>
<tr>
<td><strong>9. SPECIAL STORAGE CONDITIONS</strong></td>
</tr>
<tr>
<td>Store upright pictogram for upright storage to be included</td>
</tr>
<tr>
<td><strong>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
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</tr>
<tr>
<td>-------------------------------------------------------------</td>
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<td>Germany</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>12. MARKETING AUTHORIZATION NUMBER(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/08/442/031</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

| 14. GENERAL CLASSIFICATION FOR SUPPLY                         |

<table>
<thead>
<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date and Time of preparation:</td>
</tr>
</tbody>
</table>

| 16. INFORMATION IN BRAILLE                                   |

| 17. UNIQUE IDENTIFIER – 2D BARCODE                          |

| 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA                  |

217
| MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS |
| SACHET – PRADAXA POWDER FOR ORAL SOLUTION |

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

   Pradaxa 180.4 mg powder for oral solution

2. **METHOD OF ADMINISTRATION**

   Read the package leaflet before use.

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

6. **OTHER**
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SACHET – SUCRALOSE FOR ORAL SOLUTION</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg Sucralose for Pradaxa oral solution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. METHOD OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>6. OTHER</strong></th>
</tr>
</thead>
</table>
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 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.

Pradaxa is used in children to:
- treat blood clots and to prevent blood clots from reoccurring.

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, while having a venous or arterial line and you get heparin through this line to keep it open or while your heart beat is being restored to normal by a procedure called catheter ablation for atrial fibrillation.
- 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 are taking a combination product of glecaprevir and pibrentasvir, an antiviral medicine used to treat hepatitis C
- 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 this medicine 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 decreased kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) / foaming urine).
  - if you are older than 75 years.
  - if you are an adult patient and weigh 50 kg or less.
  - only if used for children: if the child has an infection around or within the brain.
- 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 this medicine 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.
if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

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 it is prescribed to you. See also section 3.
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- A combination product of glecaprevir and pibrentasvir (an antiviral medicine used to treat hepatitis C)
- 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 this medicine 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

Pradaxa capsules can be used in adults and children aged 8 years or older who are able to swallow the capsules whole. There are other age appropriate dose forms for the treatment of children below 8 years.

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 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.

Treatment of blood clots and prevention of blood clots from reoccurring in children

Pradaxa should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose depends on weight and age. Your doctor will determine the correct dose. Your doctor may adjust the dose as treatment progresses. Keep using all other medicines, unless your doctor tells you to stop using any.

Table 1 shows single and total daily Pradaxa doses in milligrams (mg). The doses depend on weight in kilograms (kg) and age in years of the patient.

Table 1: Dosing table for Pradaxa capsules

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Age in years</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to less than 13 kg</td>
<td>8 to less than 9 years</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>13 to less than 16 kg</td>
<td>8 to less than 11 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>16 to less than 21 kg</td>
<td>8 to less than 14 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>21 to less than 26 kg</td>
<td>8 to less than 16 years</td>
<td>130</td>
<td>300</td>
</tr>
<tr>
<td>26 to less than 31 kg</td>
<td>8 to less than 18 years</td>
<td>130</td>
<td>300</td>
</tr>
<tr>
<td>31 to less than 41 kg</td>
<td>8 to less than 18 years</td>
<td>185</td>
<td>370</td>
</tr>
<tr>
<td>41 to less than 51 kg</td>
<td>8 to less than 18 years</td>
<td>220</td>
<td>440</td>
</tr>
<tr>
<td>51 to less than 61 kg</td>
<td>8 to less than 18 years</td>
<td>260</td>
<td>520</td>
</tr>
<tr>
<td>61 to less than 71 kg</td>
<td>8 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>71 to less than 81 kg</td>
<td>8 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>81 kg or greater</td>
<td>10 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
</tbody>
</table>

Single doses requiring combinations of more than one capsule:

- 300 mg: two 150 mg capsules or four 75 mg capsules
- 260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
- 220 mg: as two 110 mg capsules
185 mg: as one 75 mg plus one 110 mg capsule
150 mg: as one 150 mg capsule or
two 75 mg capsules

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 of this medicine increases the risk of bleeding. Contact your doctor immediately if you have taken too many 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.

Treatment of blood clots and prevention of blood clots from reoccurring in children
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 double a dose to make up for a forgotten dose.

**If you stop taking Pradaxa**

Take Pradaxa exactly as prescribed. Do not stop taking this medicine 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 blood cells
- 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
- Decreases in the number or even lack of white blood cells (which help to fight infections)
- Hair loss

Treatment of blood clots and prevention of blood clots from reoccurring in children

Common (may affect up to 1 in 10 people):
- A fall in the number of red cells in the blood
- A fall in the number of platelets in the blood
- 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
- Haematoma formation
- Nosebleed
- Reflux of gastric juice into the gullet
- Vomiting
- Feeling sick
- Frequent loose or liquid bowel movements
- Indigestion
- Hair loss
- Liver enzymes increased

Uncommon (may affect up to 1 in 100 people):
- Decrease in the number of white blood cells (which help to fight infections)
- Bleeding may happen into the stomach or bowel, from the brain, 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
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A decrease in the proportion of blood cells
- Itching
- Coughing of blood or blood stained sputum
- Belly ache or stomach ache
- Inflammation of the gullet and stomach
- Allergic reaction
- Difficulty in swallowing
- 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):
- Lack of white blood cells (which help to fight infections)
- Serious allergic reaction which causes difficulty in breathing or dizziness
Serious allergic reaction which causes swelling of the face or throat
- Difficulty in breathing or wheezing
- Bleeding
- Bleeding may happen into a joint or from an injury, 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
- Bleeding may happen from piles
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Unusual laboratory test results on liver function

**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 75 mg dabigatran etexilate (as mesilate).
- 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 (approx. 18 x 6 mm) 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 hard capsule.

This medicine is available in packs containing 10 x 1, 30 x 1 or 60 x 1 hard capsules in aluminium perforated unit dose blisters. Furthermore, Pradaxa is available in packs containing 60 x 1 hard capsules in aluminium perforated unit dose white blisters.

This medicine is 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
55216 Ingelheim am Rhein
Germany

**Manufacturer**

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

and

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
SCS Boehringer Ingelheim Comm.V
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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/
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-occurring in the vein of your legs and lungs.

Pradaxa is used in children to:
- treat blood clots and to prevent blood clots from reoccurring.

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, while having a venous or arterial line and you get heparin through this line to keep it open or while your heart beat is being restored to normal by a procedure called catheter ablation for atrial fibrillation. 
- 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 have a severely reduced liver function or liver disease which could possibly cause death. 
- if you are taking a combination product of glecaprevir and pibrentasvir, an antiviral medicine used to treat hepatitis C 
- 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 this medicine 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 decreased kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) /foaming urine).
  - if you are older than 75 years.
  - if you are an adult patient and weigh 50 kg or less.
  - only if used for children: if the child has an infection around or within the brain.

- 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 this medicine 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.

- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

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 it is prescribed to you. See section 3.
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- A combination product of glecaprevir and pibrentasvir (an antiviral medicine used to treat hepatitis C)
- 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 this medicine 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

Pradaxa capsules can be used in adults and children aged 8 years or older who are able to swallow the capsules whole. There are other age appropriate dose forms for the treatment of children below 8 years.
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 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.

**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**

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 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 220 mg taken as one 110 mg capsule twice a day.

You can continue to take this medicine if your heart beat needs to be restored to normal by a procedure called cardioversion. Take Pradaxa as your physician has told you.

If a medical device (stent) has been deployed in a blood vessel to keep it open in a procedure called percutaneous coronary intervention with stenting, you can be treated with Pradaxa after your physician has decided that normal control of blood coagulation is achieved. Take Pradaxa as your physician has told you.
Treatment of blood clots and prevention of blood clots from reoccurring in children

**Pradaxa should be taken twice daily**, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose depends on weight and age. Your doctor will determine the correct dose. Your doctor may adjust the dose as treatment progresses. Keep using all other medicines, unless your doctor tells you to stop using any.

Table 1 shows single and total daily Pradaxa doses in milligrams (mg). The doses depend on weight in kilograms (kg) and age in years of the patient.

**Table 1: Dosing table for Pradaxa capsules**

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Age in years</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to less than 13 kg</td>
<td>8 to less than 9 years</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>13 to less than 16 kg</td>
<td>8 to less than 11 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>16 to less than 21 kg</td>
<td>8 to less than 14 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>21 to less than 26 kg</td>
<td>8 to less than 16 years</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>26 to less than 31 kg</td>
<td>8 to less than 18 years</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>31 to less than 41 kg</td>
<td>8 to less than 18 years</td>
<td>185</td>
<td>370</td>
</tr>
<tr>
<td>41 to less than 51 kg</td>
<td>8 to less than 18 years</td>
<td>220</td>
<td>440</td>
</tr>
<tr>
<td>51 to less than 61 kg</td>
<td>8 to less than 18 years</td>
<td>260</td>
<td>520</td>
</tr>
<tr>
<td>61 to less than 71 kg</td>
<td>8 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>71 to less than 81 kg</td>
<td>8 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>81 kg or greater</td>
<td>10 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
</tbody>
</table>

Single doses requiring combinations of more than one capsule:
- 300 mg: two 150 mg capsules or four 75 mg capsules
- 260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
- 220 mg: as two 110 mg capsules
- 185 mg: as one 75 mg plus one 110 mg capsule
- 150 mg: as one 150 mg capsule or two 75 mg capsules

**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

![](image)

Tear off one individual blister from the blister card along the perforated line
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 of this medicine increases the risk of bleeding. Contact your doctor immediately if you have taken too many 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.

Use in adults: 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
Use in children: Treatment of blood clots and prevention of blood clots from reoccurring
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 double a dose to make up for a forgotten dose.

If you stop taking Pradaxa

Take Pradaxa exactly as prescribed. Do not stop taking this medicine 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 blood cells
- 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
- Decreases in the number or even lack of white blood cells (which help to fight infections)
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, 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 blood cells
- 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
- Decreases in the number or even lack of white blood cells (which help to fight infections)
- Hair loss

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 (incl. ulcer in the gullet)
- 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

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 decrease in the proportion of blood cells
- Decreases in the number or even lack of white blood cells (which help to fight infections)
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems
- Hair loss

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.

Treatment of blood clots and prevention of blood clots from reoccurring in children

Common (may affect up to 1 in 10 people):
- A fall in the number of red cells in the blood
- A fall in the number of platelets in the blood
- 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
- Haematoma formation
- Nosebleed
- Reflux of gastric juice into the gullet
- Vomiting
- Feeling sick
- Frequent loose or liquid bowel movements
- Indigestion
- Hair loss
Liver enzymes increased

Uncommon (may affect up to 1 in 100 people):  
- Decrease in the number of white blood cells (which help to fight infections)
- Bleeding may happen into the stomach or bowel, from the brain, 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
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A decrease in the proportion of blood cells
- Itching
- Coughing of blood or blood stained sputum
- Belly ache or stomach ache
- Inflammation of the gullet and stomach
- Allergic reaction
- Difficulty in swallowing
- 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):
- Lack of white blood cells (which help to fight infections)
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Difficulty in breathing or wheezing
- Bleeding
- Bleeding may happen into a joint or from an injury, 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
- Bleeding may happen from piles
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Unusual laboratory test results on liver function

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 110 mg dabigatran etexilate (as mesilate).
- The other ingredients are tartaric acid, acacia, hypromellose, dimeticone 350, talc, and hydroxypropylcellulose.
- The capsule shell contains carrageenan, potassium chloride, titanium dioxide, indigo carmine, 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 (approx. 19 x 7 mm) 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 hard capsule.

This medicine is available in packs containing 10 x 1, 30 x 1 or 60 x 1 hard 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 hard capsules in aluminium perforated unit dose white blisters.

This medicine is 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/
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.

Pradaxa is used in children to:
- treat blood clots and to prevent blood clots from reoccurring.

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, while having a venous or arterial line and you get heparin through this line to keep it open or while your heart beat is being restored to normal by a procedure called catheter ablation for atrial fibrillation.
- 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 are taking a combination product of glecaprevir and pibrentasvir, an antiviral medicine used to treat hepatitis C.
- 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 this medicine 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 decreased kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) / foaming urine).
  - if you are older than 75 years.
  - if you are an adult patient and weigh 50 kg or less.
  - only if used for children: if the child has an infection around or within the brain.

- 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 this medicine 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.

- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

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 may tell you to use a reduced dose of Pradaxa depending on the condition for which it is prescribed to you. See section 3.
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- A combination product of glecaprevir and pibrentasvir (an antiviral medicine used to treat hepatitis C)
- 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 this medicine 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

Pradaxa capsules can be used in adults and children aged 8 years or older who are able to swallow the capsules whole. There are other age appropriate dose forms for the treatment of children below 8 years.

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 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.

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 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 220 mg taken as one 110 mg capsule twice a day.

You can continue to take this medicine if your heart beat needs to be restored to normal by a procedure called cardioversion or by a procedure called catheter ablation for atrial fibrillation. Take Pradaxa as your physician has told you.

If a medical device (stent) has been deployed in a blood vessel to keep it open in a procedure called percutaneous coronary intervention with stenting, you can be treated with Pradaxa after your physician has decided that normal control of blood coagulation is achieved. Take Pradaxa as your physician has told you.

Treatment of blood clots and prevention of blood clots from reoccurring in children

Pradaxa should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose depends on weight and age. Your doctor will determine the correct dose. Your doctor may adjust the dose as treatment progresses. Keep using all other medicines, unless your doctor tells you to stop using any.

Table 1 shows single and total daily Pradaxa doses in milligrams (mg). The doses depend on weight in kilograms (kg) and age in years of the patient.

Table 1: Dosing table for Pradaxa capsules

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Age in years</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to less than 13 kg</td>
<td>8 to less than 9 years</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>13 to less than 16 kg</td>
<td>8 to less than 11 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>16 to less than 21 kg</td>
<td>8 to less than 14 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>21 to less than 26 kg</td>
<td>8 to less than 16 years</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>26 to less than 31 kg</td>
<td>8 to less than 18 years</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>31 to less than 41 kg</td>
<td>8 to less than 18 years</td>
<td>185</td>
<td>370</td>
</tr>
<tr>
<td>41 to less than 51 kg</td>
<td>8 to less than 18 years</td>
<td>220</td>
<td>440</td>
</tr>
<tr>
<td>51 to less than 61 kg</td>
<td>8 to less than 18 years</td>
<td>260</td>
<td>520</td>
</tr>
<tr>
<td>61 to less than 71 kg</td>
<td>8 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>71 to less than 81 kg</td>
<td>8 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>81 kg or greater</td>
<td>10 to less than 18 years</td>
<td>300</td>
<td>600</td>
</tr>
</tbody>
</table>

Single doses requiring combinations of more than one capsule:
- 300 mg: two 150 mg capsules or four 75 mg capsules
260 mg: one 110 mg plus one 150 mg capsule or one 110 mg plus two 75 mg capsules
220 mg: as two 110 mg capsules
185 mg: as one 75 mg plus one 110 mg capsule
150 mg: as one 150 mg capsule or two 75 mg capsules

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 of this medicine increases the risk of bleeding. Contact your doctor immediately if you have taken too many 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 double a dose to make up for a forgotten dose.
If you stop taking Pradaxa

Take Pradaxa exactly as prescribed. Do not stop taking this medicine 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 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, 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 blood cells
- 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
- Decreases in the number or even lack of white blood cells (which help to fight infections)
- Hair loss

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 (incl. ulcer in the gullet)
- 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

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 decrease in the proportion of blood cells
- Decreases in the number or even lack of white blood cells (which help to fight infections)
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems
- Hair loss

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.

Treatment of blood clots and prevention of blood clots from reoccurring in children

Common (may affect up to 1 in 10 people):
- A fall in the number of red cells in the blood
- A fall in the number of platelets in the blood
- 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
- Haematoma formation
- Nosebleed
- Reflux of gastric juice into the gullet
- Vomiting
- Feeling sick
- Frequent loose or liquid bowel movements
- Indigestion
- Hair loss
- Liver enzymes increased

Uncommon (may affect up to 1 in 100 people):
- Decrease in the number of white blood cells (which help to fight infections)
- Bleeding may happen into the stomach or bowel, from the brain, 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
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A decrease in the proportion of blood cells
- Itching
- Coughing of blood or blood stained sputum
- Belly ache or stomach ache
- Inflammation of the gullet and stomach
- Allergic reaction
- Difficulty in swallowing
- 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):
- Lack of white blood cells (which help to fight infections)
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Difficulty in breathing or wheezing
- Bleeding
- Bleeding may happen into a joint or from an injury, 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
- Bleeding may happen from piles
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Unusual laboratory test results on liver function
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 150 mg dabigatran etexilate (as mesilate).
- The other ingredients are tartaric acid, acacia, hypromellose, dimeticone 350, talc, and hydroxypropylcellulose.
- The capsule shell contains carrageenan, potassium chloride, titanium dioxide, indigo carmine, 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 (approx. 22 x 8 mm) 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 hard capsule.

This medicine is available in packs containing 10 x 1, 30 x 1 or 60 x 1 hard 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 hard capsules in aluminium perforated unit dose white blisters.

This medicine is also available in polypropylene (plastic) bottles with 60 hard capsules.

Not all pack sizes may be marketed.
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This leaflet was last approved in

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

Pradaxa 20 mg coated granules
Pradaxa 30 mg coated granules
Pradaxa 40 mg coated granules
Pradaxa 50 mg coated granules
Pradaxa 110 mg coated granules
Pradaxa 150 mg coated granules
dabigatran etexilate

Read all of this leaflet carefully before your child starts 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 child’s doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child’s.
- If your child gets any side effects, talk to your child’s 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 your child takes 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 children to treat blood clots and to prevent blood clots from reoccurring.

2. What you need to know before your child takes Pradaxa

Do not use Pradaxa
- if your child is allergic to dabigatran etexilate or any of the other ingredients of this medicine (listed in section 6).
- if your child has severely reduced kidney function.
- if your child is currently bleeding.
- if your child has 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 your child has an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if your child is given 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 your child gets heparin through this line to keep it open.
- if your child has a severely reduced liver function or liver disease which could possibly cause death.
- if your child is given oral ketoconazole or itraconazole, medicines to treat fungal infections.
- if your child is given oral cyclosporine, a medicine to prevent organ rejection after transplantation.
- if your child is given dronedarone, a medicine used to treat abnormal heart beat.
- if your child is given a combination product of glecaprevir and pibrentasvir, an antiviral medicine used to treat hepatitis C.
- if your child has received an artificial heart valve which requires permanent blood thinning.

Warnings and precautions

Talk to your child’s doctor before you give your child Pradaxa. You may also need to talk to your child’s doctor during treatment with this medicine if your child experiences symptoms or if your child has to undergo surgery.

Tell your child’s doctor if your child has or has had any medical conditions or illnesses, in particular any of those included in the following list:

- if your child has an increased bleeding risk, such as:
  - if your child has been recently bleeding.
  - if your child has had a surgical tissue removal (biopsy) in the past month.
  - if your child has had a serious injury (e.g. a bone fracture, head injury or any injury requiring surgical treatment).
  - if your child is suffering from an inflammation of the gullet or stomach.
  - if your child has problems with reflux of gastric juice into the gullet.
  - if your child is receiving medicines which could increase the risk of bleeding. See 'Other medicines and Pradaxa' below.
  - if your child is given anti-inflammatory medicines such as diclofenac, ibuprofen, piroxicam.
  - if your child is suffering from an infection of the heart (bacterial endocarditis).
  - if you know your child has decreased kidney function, or your child is suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) / foaming urine).
  - if your child has an infection around or within the brain.
- if your child has had a heart attack or if your child has been diagnosed with conditions that increase the risk to develop a heart attack.
- if your child has a liver disease that is associated with changes in the blood tests. The use of this medicine is not recommended in this case.

Take special care with Pradaxa

- if your child needs 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 give Pradaxa before and after the operation exactly at the times you have been told by your child’s doctor.

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

- if your child falls or injures himself/herself during treatment, especially if your child hits his/her head. Please seek urgent medical attention. Your child may need to be checked by a doctor, as your child may be at increased risk of bleeding.
if you know that your child has a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your child’s doctor who will decide if the treatment may need to be changed.

Other medicines and Pradaxa

Tell your child’s doctor or pharmacist if your child is given or has recently been given other medicines. In particular you should tell your child’s doctor before taking Pradaxa, if your child is given 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)
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- A combination product of glecaprevir and pibrentasvir (an antiviral medicine used to treat hepatitis C)
- Anti-inflammatory and pain reliever medicines (e.g. acetylsalicylic acid, ibuprofen, diclofenac)
- Medicines to treat fungal infections (e.g. ketoconazole, itraconazole), unless they are only applied to the skin
- 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)

Pradaxa with food and drink

Do not mix Pradaxa coated granules with milk or soft food containing milk products. Only use this medicine with apple juice or one of the soft foods mentioned in the instructions for use at the end of the package leaflet.

Pregnancy and breast-feeding

This medicine is intended to be used in children below the age of 12 years. Information regarding pregnancy and breast-feeding may not be relevant in the context of your child’s treatment.

The effects of Pradaxa on pregnancy and the unborn child are not known. A pregnant woman should not take this medicine unless her doctor advises her that it is safe to do so. A woman of child-bearing age should avoid becoming pregnant while she is taking Pradaxa.

Breast-feeding should be stopped during treatment with Pradaxa.

Driving and using machines

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

3. How to take Pradaxa

Pradaxa coated granules can be used for children below 12 years as soon as they are able to swallow soft food. There are other age appropriate dose forms for the treatment of babies below 12 months and children aged 8 years or older.

Always give this medicine exactly as your child’s doctor has told you. Check with your child’s doctor if you are not sure.
Pradaxa should be taken 
twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose depends on weight and age. Your child’s doctor will determine the correct dose. Your child’s doctor may adjust the dose as treatment progresses. Your child must keep using all other medicines, unless your child’s doctor tells you to stop using any.

Table 1 shows single and total daily Pradaxa doses in milligrams (mg) for patients below 12 months. The doses depend on weight in kilograms (kg) and age in months of the patient.

Table 1: Dosing table for Pradaxa coated granules for patients below 12 months

<table>
<thead>
<tr>
<th>Weight in kg / Age in MONTHS</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 to less than 3 kg / 4 to less than 5 months</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>3 to less than 4 kg / 3 to less than 6 months</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>4 to less than 5 kg / 1 to less than 3 months</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>3 to less than 8 months</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>8 to less than 10 months</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>5 to less than 7 kg / 0 to less than 1 months</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>1 to less than 5 months</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>5 to less than 8 months</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>8 to less than 12 months</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>7 to less than 9 kg / 3 to less than 4 months</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>4 to less than 9 months</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>9 to less than 12 months</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>9 to less than 11 kg / 5 to less than 6 months</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>6 to less than 11 months</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>11 to less than 12 months</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>11 to less than 13 kg / 8 to less than 10 months</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>10 to less than 12 months</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>13 to less than 16 kg / 10 to less than 11 months</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>11 to less than 12 months</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

20 mg: One 20 mg sachet
30 mg: One 30 mg sachet
40 mg: One 40 mg sachet
50 mg: One 50 mg sachet
60 mg: Two 30 mg sachets
70 mg: One 30 mg plus one 40 mg sachet
80 mg: Two 40 mg sachets
100 mg: Two 50 mg sachets

Table 2 shows single and total daily Pradaxa doses in milligrams (mg) for patients from 1 year to less than 12 years. The doses depend on weight in kilograms (kg) and age in years of the patient.
Table 2: Dosing table for Pradaxa coated granules for patients from 1 year to less than 12 years

<table>
<thead>
<tr>
<th>Weight in kg / Age in YEARS</th>
<th>Single dose in mg</th>
<th>Total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to less than 7 kg / 1 to less than 2 years</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>7 to less than 9 kg / 1 to less than 2 years</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>2 to less than 4 years</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>9 to less than 11 kg / 1 to less than 1.5 years</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>1.5 to less than 7 years</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>11 to less than 13 kg / 1 to less than 1.5 years</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>1.5 to less than 2.5 years</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>2.5 to less than 9 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>13 to less than 16 kg / 1 to less than 1.5 years</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>1.5 to less than 2 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>2 to less than 12 years</td>
<td>140</td>
<td>280</td>
</tr>
<tr>
<td>16 to less than 21 kg / 1 to less than 2 years</td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>2 to less than 12 years</td>
<td>140</td>
<td>280</td>
</tr>
<tr>
<td>21 to less than 26 kg / 1.5 to less than 2 years</td>
<td>140</td>
<td>280</td>
</tr>
<tr>
<td>2 to less than 12 years</td>
<td>180</td>
<td>360</td>
</tr>
<tr>
<td>26 to less than 31 kg / 2.5 to less than 12 years</td>
<td>180</td>
<td>360</td>
</tr>
<tr>
<td>31 to less than 41 kg / 2.5 to less than 12 years</td>
<td>220</td>
<td>440</td>
</tr>
<tr>
<td>41 to less than 51 kg / 4 to less than 12 years</td>
<td>260</td>
<td>520</td>
</tr>
<tr>
<td>51 to less than 61 kg / 5 to less than 12 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>61 to less than 71 kg / 6 to less than 12 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>71 to less than 81 kg / 7 to less than 12 years</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>above 81 kg / 10 to less than 12 years</td>
<td>300</td>
<td>600</td>
</tr>
</tbody>
</table>

Convenient sachet combinations to achieve the single doses recommended in the dosing table are provided below. Other combinations are possible.

- 50 mg: One 50 mg sachet
- 60 mg: Two 30 mg sachets
- 70 mg: One 30 mg plus one 40 mg sachet
- 80 mg: Two 40 mg sachets
- 100 mg: Two 50 mg sachets
- 110 mg: One 110 mg sachet
- 140 mg: One 30 mg plus one 110 mg sachet
- 180 mg: One 30 mg plus one 150 mg sachet
- 220 mg: Two 110 mg sachets
- 260 mg: One 110 mg plus one 150 mg sachet
- 300 mg: Two 150 mg sachets

Method and route of administration

This medicine is given together with apple juice or one of the soft food options mentioned in the instructions for use. Do not mix this medicine with milk or soft food containing milk products.

Detailed instructions for the use of this medicine are provided in ‘Instructions for use’ at the end of the package leaflet.

Change of anticoagulant treatment

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

If you give more Pradaxa than you should

Taking too much of this medicine increases the risk of bleeding. Contact your child’s doctor immediately if you have given too much of it. Specific treatment options are available.

If you forget to give your child Pradaxa
A forgotten dose can still be given 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 give a double dose to make up for a forgotten dose. If a dose has only been taken partially, do not attempt to administer a second dose at that time-point. Give the next dose as scheduled approximately 12 hours later.

If you stop giving Pradaxa

Give Pradaxa exactly as prescribed. Do not stop giving this medicine without talking to your child’s doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early. Contact your child’s doctor if your child experiences indigestion after giving Pradaxa.

If you have any further questions on the use of this medicine, ask your child’s 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 your child experiences any bleeding event that does not stop by itself or if your child experiences signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your child’s doctor immediately. Your child’s doctor may decide to keep your child under closer observation or change the medicine.

Tell your child’s doctor immediately, if your child experiences 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 number of red cells in the blood
- A fall in the number of platelets in the blood
- 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
- Haematoma formation
- Nosebleed
- Reflux of gastric juice into the gullet
- Vomiting
- Feeling sick
- Frequent loose or liquid bowel movements
- Indigestion
- Hair loss
- Liver enzymes increased

Uncommon (may affect up to 1 in 100 people):
- Decrease in the number of white blood cells (which help to fight infections)
- Bleeding may happen into the stomach or bowel, from the brain, 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
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A decrease in the proportion of blood cells
- Itching
- Coughing of blood or blood stained sputum
- Belly ache or stomach ache
- Inflammation of the gullet and stomach
- Allergic reaction
- Difficulty in swallowing
- 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):
- Lack of white blood cells (which help to fight infections)
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Difficulty in breathing or wheezing
- Bleeding
- Bleeding may happen into a joint or from an injury, 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
- Bleeding may happen from piles
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Unusual laboratory test results on liver function

**Reporting of side effects**
If your child gets 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 after “EXP”. The expiry date refers to the last day of that month.

Before first use, do not open the aluminium bag containing the sachets with the Pradaxa coated granules in order to protect from moisture.

Once the aluminium bag containing the sachets with the coated granules and the desiccant is opened, the medicine must be used within 6 months. The opened sachet cannot be stored and must be used immediately after opening.

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 sachet of Pradaxa 20 mg coated granules contains coated granules with 20 mg dabigatran etexilate (as mesilate).
- The active substance is dabigatran. Each sachet of Pradaxa 30 mg coated granules contains coated granules with 30 mg dabigatran etexilate (as mesilate).
- The active substance is dabigatran. Each sachet of Pradaxa 40 mg coated granules contains coated granules with 40 mg dabigatran etexilate (as mesilate).
- The active substance is dabigatran. Each sachet of Pradaxa 50 mg coated granules contains coated granules with 50 mg dabigatran etexilate (as mesilate).
The active substance is dabigatran. Each sachet of Pradaxa 110 mg coated granules contains coated granules with 110 mg dabigatran etexilate (as mesilate).

- The active substance is dabigatran. Each sachet of Pradaxa 150 mg coated granules contains coated granules with 150 mg dabigatran etexilate (as mesilate).

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

What Pradaxa looks like and contents of the pack

The sachets of Pradaxa coated granules contain yellowish coated granules.

Each pack of this medicine contains an aluminium bag which in turn contains 60 silver-coloured aluminium sachets with Pradaxa coated granules and a desiccant (labelled “DO NOT EAT” including pictogram and “SILICA GEL”).

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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/
Instructions for use

Do not administer Pradaxa coated granules
- via syringes or feeding tubes
- with other than the soft foods or apple juice as indicated below

Administer Pradaxa coated granules either with soft foods or apple juice. The instructions are provided below under A) for soft foods and B) for apple juice.

The prepared medicine should be given before meals in order to ensure that the patient takes the full dose.

Administer the prepared medicine to the patient immediately or within 30 minutes after mixing. Do not give this medicine if it has been in contact with the food or apple juice for more than 30 minutes.

In case of an incomplete intake of the prepared medicine, do not apply a second dose, wait until the next dosing time-point.

A) Administration of Pradaxa coated granules with soft foods

The food should be at room temperature before mixing with the coated granules. The medicine can be administered with one of the following soft foods:
- Mashed carrots
- Apple sauce (for administration with apple juice see B))
- Mashed banana

Do not use soft food containing milk products.

Step 1 – Prepare cup or bowl
- Transfer two teaspoons of the soft food into a small cup or bowl.

Step 2 – Collect sachet(s)
- Upon first opening, open the silver aluminium bag by cutting at the top using scissors. The aluminium bag includes 60 silver-coloured sachets (medicine) and one desiccant with the imprint “DO NOT EAT” including pictogram and “SILICA GEL”.

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- Do not open or consume the desiccant.

<table>
<thead>
<tr>
<th>Step 3 – Open sachet(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Take the sachet containing the Pradaxa coated granules.</td>
</tr>
<tr>
<td>• Tap the sachet on the table to ensure that the contents settle to the bottom.</td>
</tr>
<tr>
<td>• Keep the sachet in an upright position.</td>
</tr>
<tr>
<td>• Open the sachet by cutting at the top using scissors.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4 – Pour sachet(s) content</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Empty the entire content of the sachet into the small cup or bowl containing the soft food.</td>
</tr>
<tr>
<td>• Repeat Steps 3 and 4 if more than one sachet is needed.</td>
</tr>
</tbody>
</table>
Step 5 – Stir soft food to mix coated granules
- Stir soft food with the feeding spoon to thoroughly mix the coated granules with the soft food.

Step 6 – Administer soft food
- Administer the soft food with the coated granules to the patient immediately using the feeding spoon.
- Assure that all soft food is eaten.

B) Administration of Pradaxa coated granules with apple juice

Step 1 – Have a cup of apple juice ready before the next step

Step 2 – Collect sachet(s)
- Upon first opening, open the silver aluminium bag by cutting at the top using scissors. The aluminium bag includes 60 silver-coloured sachets (medicine) and one desiccant with the imprint “DO NOT EAT” including pictogram and “SILICA GEL”.
- Do not open or consume the desiccant.
Collect the required number of sachets with Pradaxa coated granules according to the prescribed dose.

Put the unused sachets back into the aluminium bag.

Step 3 – Open sachet(s)
- Take the sachet containing the Pradaxa coated granules.
- Tap the sachet on the table to ensure that the contents settle to the bottom.
- Keep the sachet in an upright position.
- Open the sachet by cutting at the top using scissors.

Step 4 – Administer Pradaxa coated granules with apple juice
- Administer all of the coated granules directly from the sachet or using a feeding spoon into the child’s mouth and offer the child as much apple juice as needed to swallow the coated granules.
- Inspect child’s mouth to ensure that all coated granules are swallowed.
- Optional: If the Pradaxa coated granules are mixed in the apple juice cup, start with a small amount of apple juice (that your child is likely to drink completely) and ensure that all coated granules are taken. If coated granules are sticking to the cup, add another small amount of apple juice and again apply to your child. Repeat until no remaining coated granules are sticking to the cup.
Package leaflet: Information for the patient
Pradaxa 6.25 mg/mL powder and solvent for oral solution
dabigatran etexilate

Read all of this leaflet carefully before your child starts 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 child’s doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child’s.
- If your child gets any side effects, talk to your child’s 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 your child takes 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 children to treat blood clots and to prevent blood clots from reoccurring.
Pradaxa powder and solvent for oral solution should not be used in children aged 1 year or older.

2. What you need to know before your child takes Pradaxa
Do not use Pradaxa
- if your child is allergic to dabigatran etexilate or any of the other ingredients of this medicine (listed in section 6).
- if your child has severely reduced kidney function.
- if your child is currently bleeding.
- if your child has 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 your child has an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if your child is given 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 your child gets heparin through this line to keep it open.
- if your child has a severely reduced liver function or liver disease which could possibly cause death.
- if your child is given oral ketoconazole oritraconazole, medicines to treat fungal infections.
- if your child is given oral cyclosporine, a medicine to prevent organ rejection after transplantation.
- if your child is given dronedarone, a medicine used to treat abnormal heart beat.
- if your child is given a combination product of glecaprevir and pibrentasvir, an antiviral medicine used to treat hepatitis C
- if your child has received an artificial heart valve which requires permanent blood thinning.

**Warnings and precautions**

Talk to your child’s doctor before you give your child Pradaxa. You may also need to talk to your child’s doctor during treatment with this medicine if your child experiences symptoms or if your child has to undergo surgery.

**Tell your child’s doctor** if your child has or has had any medical conditions or illnesses, in particular any of those included in the following list:

- if your child has an increased bleeding risk, such as:
  - if your child has been recently bleeding.
  - if your child has had a surgical tissue removal (biopsy) in the past month.
  - if your child has had a serious injury (e.g. a bone fracture, head injury or any injury requiring surgical treatment).
  - if your child is suffering from an inflammation of the gullet or stomach.
  - if your child has problems with reflux of gastric juice into the gullet.
  - if your child is receiving medicines which could increase the risk of bleeding. See 'Other medicines and Pradaxa' below.
  - if your child is suffering from an infection of the heart (bacterial endocarditis).
  - if you know your child has decreased kidney function, or your child is suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) / foaming urine).
  - if your child has an infection around or within the brain.
- if your child has had a heart attack or if your child has been diagnosed with conditions that increase the risk to develop a heart attack.
- if your child has a liver disease that is associated with changes in the blood tests. The use of this medicine is not recommended in this case.

**Take special care with Pradaxa**

- if your child needs 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 give Pradaxa before and after the operation exactly at the times you have been told by your child’s doctor.
- if an operation involves a catheter or injection into your child’s spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to give Pradaxa before and after the operation exactly at the times you have been told by your child’s doctor.
  - tell your child’s doctor immediately if your child gets numbness or weakness of the legs or problems with his/her bowel or bladder after the end of anaesthesia, because urgent care is necessary.
- if your child falls or injures himself/herself during treatment, especially if your child hits his/her head. Please seek urgent medical attention. Your child may need to be checked by a doctor, as your child may be at increased risk of bleeding.
- if you know that your child has a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your child’s doctor who will decide if the treatment may need to be changed.
Other medicines and Pradaxa

Tell your child’s doctor or pharmacist if your child is given or has recently been given other medicines. In particular you should tell your child’s doctor before taking Pradaxa, if your child is given 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)
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- A combination product of glecaprevir and pibrentasvir (an antiviral medicine used to treat hepatitis C)
- 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

This medicine is intended to be used in children below the age of 12 months. Information regarding pregnancy and breast-feeding will not be relevant in the context of your child’s treatment.

Driving and using machines

This medicine is intended to be used in children below the age of 12 months. Information regarding driving and using machines will not be relevant in the context of your child’s treatment.

3. How to take Pradaxa

Pradaxa powder and solvent for oral solution should only be used in children below 1 year. There are other age appropriate dose forms for the treatment of children and adolescents aged 1 year or older.

Always give this medicine exactly as your child’s doctor has told you. Check with your child’s doctor if you are not sure.

Pradaxa should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose depends on weight and age. Your child’s doctor will determine the correct dose. Your child’s doctor may adjust the dose as treatment progresses. Your child must keep using all other medicines, unless your child’s doctor tells you to stop using any.

Table 1 shows single and total daily Pradaxa doses in millilitres (mL). The doses depend on weight in kilograms (kg) and age in months of the patient:

<table>
<thead>
<tr>
<th>Weight /age combinations</th>
<th>Single dose in mL</th>
<th>Total daily dose in mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight in kg</td>
<td>Age in months</td>
<td></td>
</tr>
<tr>
<td>2.5 to less than 3 kg</td>
<td>less than 4 months</td>
<td>2</td>
</tr>
</tbody>
</table>
Pradaxa oral solution is prepared from Pradaxa powder, a sweetener (sucralose) and a solvent. It is administered with a dosing pipette into your child’s mouth. Pradaxa oral solution should not be mixed with milk, other beverages or food.

Detailed instructions for the preparation of the oral solution and the administration with the dosing pipette are provided in ‘Instructions for use’ at the end of the package leaflet.

The instructions for use contain all steps necessary for the correct preparation of this medicine and its administration to the patient. This medicine should be prepared by a doctor, nurse or pharmacist. Lay caregivers can prepare the oral solution if the healthcare professional determines that it is appropriate. In this case all steps of the instructions for use should be followed.

In case your doctor, nurse or pharmacist has provided you the prepared oral solution, please follow steps 11-22 of the instructions for use.

Change of anticoagulant treatment

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

If you give more Pradaxa than you should

Taking too much of this medicine increases the risk of bleeding. Contact your child’s doctor immediately if you have given too much of it. Specific treatment options are available.
If you forget to give your child Pradaxa

A forgotten dose can still be given 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 give a double dose to make up for a forgotten dose. If a dose has only been taken partially, do not attempt to administer a second dose at that time-point. Give the next dose as scheduled approximately 12 hours later.

If you stop giving Pradaxa

Give Pradaxa exactly as prescribed. Do not stop giving this medicine without talking to your child’s doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early. Contact your child’s doctor if your child experiences indigestion after giving Pradaxa.

If you have any further questions on the use of this medicine, ask your child’s 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 your child experiences any bleeding event that does not stop by itself or if your child experiences signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your child’s doctor immediately. Your child’s doctor may decide to keep your child under closer observation or change the medicine.

Tell your child’s doctor immediately, if your child experiences 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 number of red cells in the blood
- A fall in the number of platelets in the blood
- 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
- Haematoma formation
- Nosebleed
- Reflux of gastric juice into the gullet
- Vomiting
- Feeling sick
- Frequent loose or liquid bowel movements
- Indigestion
- Hair loss
- Liver enzymes increased

Uncommon (may affect up to 1 in 100 people):
- Decrease in the number of white blood cells (which help to fight infections)
- Bleeding may happen into the stomach or bowel, from the brain, 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
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A decrease in the proportion of blood cells
- Itching
- Coughing of blood or blood-stained sputum
- Belly ache or stomach ache
- Inflammation of the gullet and stomach
- Allergic reaction
- Difficulty in swallowing
- 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):
- Lack of white blood cells (which help to fight infections)
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Difficulty in breathing or wheezing
- Bleeding
- Bleeding may happen into a joint or from an injury, 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
- Bleeding may happen from piles
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Unusual laboratory test results on liver function

**Reporting of side effects**
If your child gets 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.

This medicine is prepared from three components which may have different expiry dates. Do not prepare and use this medicine after the shortest expiry date which is stated on the outer carton after “EXP”. Note that individual components may have later expiry dates. The expiry date refers to the last day of that month.

Store so that the bottle inside each individual preparation pack is upright.

Once the aluminium bag containing the sachets with the Pradaxa powder for oral solution and the desiccant is opened, the medicine must be used within 4 months. The opened sachet cannot be stored and must be used immediately after opening.

Once prepared, the oral solution in the bottle can be stored for up to 18 hours at 2-8°C (refrigerator) or, if needed, for up to 2 hours at room temperature (20-25°C). The bottles must be stored in an upright position.

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 mL of reconstituted oral solution contains 6.25 mg of dabigatran etexilate (as mesilate).

- The other ingredients of the Pradaxa powder for oral solution are mannitol and hydroxypropylcellulose.

- The solvent for Pradaxa oral solution contains tartaric acid, hydrochloric acid (for pH-adjustment) and purified water.

- The sucralose sachets contain sucralose.

What Pradaxa looks like and contents of the pack

Pradaxa powder and solvent for oral solution is supplied as several components for reconstitution in a kit that contains:

- 1 carton box containing the Pradaxa powder for oral solution.
  30 aluminium sachets are packaged in one aluminium bag that also contains a desiccant (labelled with “DO NOT EAT” including pictogram and “SILICA GEL”). Each sachet contains 180.4 mg powder for oral solution. Pradaxa powder for oral solution is a yellowish-white powder.

- 30 carton boxes which are referred to as individual preparation packs.
  Each pack contains one white aluminium sachet with 70 mg sucralose powder (white to almost white powder), one amber glass bottle with a screw-cap containing 28 mL solvent (clear, colourless solution) to prepare the oral solution, two dosing pipettes (12 mL) and one adapter for the bottle.

The co-packaged dosing pipettes and the adapter are medical devices.
On the 12 mL dosing pipette, a scale from 0 to 12 mL with 0.25 mL graduation is printed.

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This leaflet was last approved in

Other sources of information

A training video is available by scanning the QR code included in the ‘Instructions for use’ and the outer carton. The same information is also available on the following URL: www.Pradaxa-kids.com

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

Pradaxa 6.25 mg/mL powder and solvent for oral solution

Read instructions before use

You have received an oral solution kit containing 30 preparation packs and one aluminum bag containing 30 silver coloured sachets. One silver coloured sachet contains yellowish-white powder (medicine) for preparing an oral solution. The aluminum bag also contains a desiccant (labelled with “DO NOT EAT” including pictogram and “SILICA GEL”) to keep the medicine dry.

The instructions for use contain all steps necessary for the correct preparation of the oral solution and administration to the patient. The oral solution should be prepared by a doctor, nurse or pharmacist. Lay caregivers can prepare the oral solution if the treating physician determines that it is appropriate. All steps of the instructions for use should be followed. In case your doctor, nurse or pharmacist has provided you the prepared oral solution, please follow steps 11-22.

You can preserve the prepared oral solution for 2 hours at room temperature or 18 hours in a refrigerator. Give two doses per day with an interval as close to 12 hours as possible.

Supplies for preparing medicine

You will need the following supplies to prepare the medicine, included in each individual preparation pack:

A. Bottle containing 28 mL solvent.
B. Pipette adapter.
C. White (sucralose) sachet containing sweetener.
D. 2 Dosing pipettes (12 mL).

⚠️ Discard dosing pipette after use (single use only).
You will need the following other supplies, not included in each individual preparation pack:

- **E.** Silver (dabigatran etexilate) sachet containing powder (medicine), included in the aluminum bag.
- **F.** Pair of scissors (not supplied).
- **G.** Pen (not supplied).

**Warnings and Cautions**

**Read all warnings and cautions before preparing the medicine.**

**Warnings**
- Store prepared oral solution in the bottle for up to 18 hours in a refrigerator at 2°C to 8°C. The oral solution may be stored for a maximum of 2 hours at room temperature (20°C to 25°C).
- Safely throw away any unused oral solution left in the bottle after 18 hours.
- Do not prepare oral solution with liquid other than the solvent that comes in the kit.
- Do not mix prepared oral solution with milk, other beverages, baby formula or any other kind of food.
- Do not use a measuring device other than the dosing pipettes that come in your kit to measure and give a dose of this medicine.
- Do not heat oral solution.

**Cautions**
- To avoid a reduced dose of medicine, make sure to pour all contents of silver sachet (medicine) into solvent bottle.
- Take care to adjust dosing pipette carefully to the prescribed dose. Check dose before administration.
- The interval between dosing of this medicine should be as close to 12 hours as possible.
- If a dose is missed for any reason, the forgotten dose may still be taken up to 6 hours prior to the next scheduled dose.
- If a missed dose cannot be taken up to 6 hours prior to the next scheduled dose, omit the missed dose and administer the next dose as scheduled.
- Do not administer a double dose to make up for a missed individual dose or for an incomplete dose intake.
- Do not use feeding tubes.
A Prepare Oral Solution

1 Place one silver sachet (dabigatran etexilate) in an individual preparation pack

A. Place 1 silver sachet from the aluminum bag in each individual preparation pack.
B. The bag contains a desiccant (labelled with “DO NOT EAT” including pictogram and “SILICA GEL”) with silica gel to keep contents dry.

Do not use desiccant to prepare the oral solution.

C. Before each use, make sure each individual preparation pack contains:
   1 bottle, 1 silver (dabigatran etexilate) sachet, 1 white (sucralose) sachet,
   1 adapter and 2 dosing pipettes (12 mL).

If you are going to travel make sure you have completed Step 1 before travelling for all doses to be given during travel.

To avoid preparing the oral solution without medicine, it is recommended that you complete all individual preparation packs with the silver sachet at the point in time when you are preparing the first dose of a new oral solution kit.

2 Prepare bottle

D. Take the bottle with solvent out of the individual preparation pack.
E. Open bottle in an upright position by pressing down on the child resistant cap and simultaneously turning the cap counter-clockwise.
F. Leave the open bottle on the table.

3 Open silver (dabigatran etexilate) sachet

A. Take the silver (dabigatran etexilate) sachet containing powder (medicine).
B. Tap the silver sachet on the table to ensure the silver sachet contents settle to
C. Keep the silver sachet in upright position.
D. Open the silver sachet by cutting at the top using scissors.

4 Pour silver sachet contents
A. Hold and squeeze the silver sachet to ensure a circular opening.
B. Carefully pour all the content of the silver sachet (medicine) into the bottle, tapping the sachet until it is empty.

⚠️ To avoid a reduced dose of medicine, make sure to pour all contents of sachet into solvent bottle.

5 Open white (sucralose) sachet
A. Take the white (sucralose) sachet containing sweetener.
B. Tap the white sachet on the table to ensure the white sachet contents settle to the bottom.
C. Keep the white sachet in upright position.
D. Open the white sachet by cutting at the top using scissors.

6 Pour white sachet contents
A. Hold and squeeze the white sachet to ensure a circular opening.
B. Carefully pour all the content of the white sachet (sweetener) into the bottle, tapping the sachet until it is empty.
7 Insert adapter
   A. With the open bottle on the table, hold the bottle with one hand and press the pipette adapter into the bottle opening with the other hand.

⚠️ Make sure the adapter is completely inserted in bottle neck until the adapter cannot be pushed any further.

8 Close bottle and write date and time on label
   A. Tightly close the bottle with the cap (turn the cap clockwise).
   B. Assure that the cap is securely attached to avoid medicine from spilling.
   C. Write the date and time on the bottle label next to “Date and Time of preparation:”.

9 Shake bottle to dissolve medicine
   A. Shake the bottle vigorously for at least 2 minutes to dissolve the medicine powder in the solution. Use a stopwatch or clock to measure 2 minutes.

⚠️ Shaking the bottle for less than 2 minutes could lead to undissolved powder in the bottle leading to a reduced dose of the medicine.

10 Wait for 1 minute
   A. Wait for at least 1 minute after shaking bottle to let most of the bubbles disappear. Use a stopwatch or clock to measure 1 minute.
   B. Check if all powder in the bottle is dissolved. If not, shake bottle until powder (medicine) in the solution is dissolved.

⚠️ If you do not allow the bottle to sit for at least 1 minute, there may be air bubbles in the oral solution. You may not be able to measure and give the correct dose of the medicine.
B Fill Dosing Pipette

11 Check prescribed dose
Your doctor should tell you the amount (dose) of Pradaxa oral solution to give to your child in millilitres (mL).

The dose of this medicine will change based on your child’s age and weight over time as your child grows. Ask your doctor or pharmacist if you are not sure.

12 Fill dosing pipette with air
Take the empty 12 mL dosing pipette and pull back on the plunger half way to fill the dosing pipette with 7 mL of air.

13 Attach dosing pipette and push air into the bottle
A. Attach the empty dosing pipette onto the adapter until it feels secure and cannot be pushed further.
B. Press in the plunger carefully and slowly, pushing the air into the bottle.

⚠️ Push air into the bottle to avoid low-pressure problems especially with large (≥ 6 mL) volumes.

14 Fill dosing pipette
A. Turn the dosing pipette together with the bottle upside down.
B. While holding the bottle together with the dosing pipette barrel with one hand, pull the plunger to the correct dosing volume with the other hand.
C. Stop when the upper edge of the plunger is at the mark corresponding to the correct dosing volume.

15 Check dosing pipette for air

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A. If there are air bubbles in the dosing pipette, tap on the barrel of the dosing pipette to move any air bubbles to the top.
B. Slowly press up on the plunger until all air bubbles have been removed.
C. Check that the dose is correct. If not, pull back on the plunger until you get the prescribed dose.

⚠️ Leaving air bubbles in the solution in the dosing pipette leads to a reduced dose of the medicine.

16 Remove dosing pipette

A. Holding the dosing pipette by the barrel to avoid readjusting the dose by mistake, put the bottle back on the table.
B. Holding the dosing pipette by the barrel, pull the dosing pipette off of the adapter and bottle.
C. Make sure the dosing pipette is still filled with the correct dose.

Note: The plunger’s position might be different from the image.

C Administer Oral Solution

17 Position child

Position the child upright to give the oral solution.

18 Administer oral solution

You should administer the required dose to the child within 10 minutes of filling the dosing pipette.
Give two doses per day with an interval as close to 12 hours as possible.

A. Place the dosing pipette in the child's mouth, so the tip is near the inner side of the cheek.
B. Press the plunger carefully and slowly to give the child sufficient time to swallow the solution.

⚠️ Do not give the oral solution if it has been stored for more than 2 hours at room temperature.
⚠️ Discard the oral solution if it has been stored for more than 2 hours at room temperature.
⚠️ Do not store the oral solution in dosing pipette.

19 Close bottle and discard used dosing pipette

A. Leave the pipette adapter in the bottle.
B. Close the bottle tightly with the cap.

Note: Make sure that the pipette adapter is inserted completely so that you are able to close the bottle properly.
C. Discard the used dosing pipette.
D. If you will not be administering another dose from the same bottle, continue directly to Step 22 to discard the bottle.

D Store Or Discard Oral Solution

20 Store bottle in refrigerator until second dose

Place the closed bottle containing the medicine immediately in the refrigerator in an upright position.

Give two doses per day with an interval as close to 12 hours as possible. Use the oral solution within 18 hours and discard the bottle after 18 hours or after giving the second dose.

⚠️ The interval between dosing of this
The medicine should be as close to 12 hours as possible.

⚠️ The bottle with the medicine can be stored for up to 18 hours in the refrigerator. Discard bottle after 18 hours or after giving the second dose, even if there is oral solution still left in it.

21 Administer second dose

Follow these steps if the prepared medicine is used a second time about 12 hours later:

A. Remove medicine bottle from the refrigerator.
B. If the child does not like the cold medicine you can let the bottle of oral solution sit at room temperature to warm up. Once removed from the refrigerator, you must give the oral solution within 2 hours.

⚠️ Do not use microwave, hot water or other heating devices.

C. Open the bottle.
D. Collect the second dosing pipette.

⚠️ Each dosing pipette is a single use device.

E. Repeat Steps 11 through 19 to administer a second dose to the child.

22 Discard used items and bottle

A. Discard all empty used dosing pipettes and empty sachets.

⚠️ Discard dosing pipette after use (single use only).

B. Once dosing is complete, or after the medicine is beyond use (2 hours at room temperature, or 18 hours in a refrigerator), discard the closed bottle.
A training video is available by scanning the QR code.
The same information is also available on the following URL: www.Pradaxa-kids.com
Dear Patient / Caregiver of a paediatric patient,

Your / your child’s doctor has initiated treatment with Pradaxa®. In order to use Pradaxa® safely, please consider the important information in the package leaflet. As this patient alert card contains important information about your / your child’s treatment, this card should be with you / your child at all times to inform healthcare professionals about your / your child’s intake of Pradaxa®.

Pradaxa® Information for Patients / Caregivers of paediatric patients

About your / your child’s treatment
- Pradaxa® thins the blood. It is used to treat existing blood clots or to prevent the formation of dangerous blood clots.
- Follow your / your child’s doctor’s instructions when taking Pradaxa®. Never skip a dose or stop the intake of Pradaxa® without talking to your / your child’s doctor.
- Inform your / your child’s doctor about all medicines you / your child are / is currently taking.
- Inform your / your child’s doctor about the intake of Pradaxa® before any surgery / invasive procedure.
- Pradaxa® capsules can be taken with or without food. The capsule should be swallowed whole with a glass of water. The capsule must not be broken or chewed and the pellets must not be emptied from the capsule.

When to seek medical advice
- Taking Pradaxa® may increase the risk of bleeding. Speak to your / your child’s doctor immediately if you / your child experience(s) signs and symptoms of bleeding such as: 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 the urine which may be pink or brown, red/black stools, coughing up blood, vomiting blood or coffee ground like material.
- In case of fall or injury, especially if the head is hit, urgently seek medical advice.
- Do not stop intake of Pradaxa® without talking to your / your child’s doctor, if you / your child experience(s) 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 (idarucizumab) is available for adult patients. The efficacy and safety of the specific reversal agent idarucizumab have not been established in paediatric patients. For details and more advice to antagonise the anticoagulant effect of Pradaxa® please refer to the Summary of Product Characteristics of Pradaxa® and idarucizumab.
• Pradaxa® is mainly eliminated by the kidneys; adequate diuresis must be maintained. Pradaxa® is dialyzable.

Please complete this section or ask your / your child’s doctor to do it.

Patient Information

___________________________________________
Name of the patient

___________________________________________
Date of birth

___________________________________________
Indication for anticoagulation

___________________________________________
Dose of Pradaxa®
PATIENT ALERT CARD

Pradaxa® coated granules
dabigatran etexilate

- This card should be with the caregiver or the patient at all times
- Make sure to use the latest version

Dear Caregiver,

Your child’s doctor has initiated treatment with Pradaxa®. In order to use Pradaxa® safely, please consider the important information in the package leaflet. As this patient alert card contains important information about your child’s treatment, this card should be with you or your child at all times to inform healthcare professionals about your child’s intake of Pradaxa®.

Pradaxa® Information for Caregivers

About your child’s treatment
- Pradaxa® thins the blood. It is used to treat existing blood clots or to prevent the formation of dangerous blood clots.
- Follow your child’s doctor’s instructions for Pradaxa® use. Always administer the prescribed dose, never skip a dose or stop the use of Pradaxa® without talking to your child’s doctor.
- Inform your child’s doctor about all medicines your child is currently taking.
- Inform your child’s doctor about your child’s intake of Pradaxa® before any surgery/invasive procedure.
- Pradaxa® coated granules should be administered with soft food or apple juice according to the instructions for use in the package leaflet. Do not use soft food containing milk products.
- Do not administer Pradaxa® coated granules via syringes or feeding tubes.

When to seek medical advice
- Taking Pradaxa® may increase the risk of bleeding. Speak to your child’s doctor immediately if your child experiences any signs and symptoms of bleeding such as: swelling, discomfort, unusual pain or headache, dizziness, paleness, weakness, unusual bruising, nosebleeds, bleeding of gums, unusually long bleeding cuts, abnormal menstrual flow or vaginal bleeding, blood in the urine which may be pink or brown, red/black stools, coughing up blood, vomiting blood or coffee ground like material.
- If your child falls or injures herself/himself, especially if she/he hits her/his head, urgently seek medical advice.
- Do not stop giving Pradaxa® without talking to your child’s doctor, if your child experiences 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.
- Pradaxa® is mainly eliminated by the kidneys; adequate diuresis must be maintained. Pradaxa® is dialyzable. See Summary of Product Characteristics.
Please complete this section or ask your child’s doctor to do it.

Patient Information

____________________________________
Name of the patient

____________________________________
Date of birth

____________________________________
Indication for anticoagulation

____________________________________
Dose of Pradaxa®
PATIENT ALERT CARD
Pradaxa® powder and solvent for oral solution
dabigatran etexilate

- This card should be with the caregiver at all times
- Make sure to use the latest version

[xxxx 20xx]
[Boehringer Ingelheim logo]

Dear Caregiver,
Your child’s doctor has initiated treatment with Pradaxa®. In order to use Pradaxa® safely, please consider the important information in the package leaflet and the instructions for use. As this patient alert card contains important information about your child’s treatment, please carry this card with you at all times to inform healthcare professionals about your child’s intake of Pradaxa®.

Pradaxa® Information for Caregivers

About your child’s treatment
- Pradaxa® thins the blood. It is used to treat existing blood clots or to prevent the formation of dangerous blood clots.
- Follow your child’s doctor’s instructions for Pradaxa® use. Always administer the prescribed dose, never skip a dose or stop the use of Pradaxa® without talking to your child’s doctor.
- Inform your child’s doctor about all medicines your child is currently taking.
- Inform your child’s doctor about your child’s intake of Pradaxa® before any surgery/invasive procedure.
- Pradaxa® oral solution should be prepared by your child’s doctor, nurse or pharmacist. You may prepare Pradaxa® oral solution if your child’s doctor thinks that this is appropriate. For administration carefully follow the instructions for use. Do not administer Pradaxa® oral solution via feeding tubes.

When to seek medical advice
- Taking Pradaxa® may increase the risk of bleeding. Speak to your child’s doctor immediately if your child experiences any signs and symptoms of bleeding such as: swelling, discomfort, unusual pain or headache, dizziness, paleness, weakness, unusual bruising, nosebleeds, bleeding of gums, unusually long bleeding cuts, vaginal bleeding, blood in the urine which may be pink or brown, red/black stools, coughing up blood, vomiting blood or coffee ground like material.
- If your child falls or injures herself/himself, especially if she/he hits her/his head, urgently seek medical advice.
- Do not stop giving Pradaxa® without talking to your child’s doctor, if your child experiences 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.
- Pradaxa® is mainly eliminated by the kidneys; adequate diuresis must be maintained. Pradaxa® is dialyzable. See Summary of Product Characteristics.
Please complete this section or ask your child’s doctor to do it.

Patient Information

Name of the patient

Date of birth

Indication for anticoagulation

Dose of Pradaxa®