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| Pradaxa 75 | Prescribing Information |
| Boehringer Ingelheim | January 2022 |



PRADAXA 75
Dabigatran Etexilate 75 mg
Hard Capsules
PRESCRIBING INFORMATION

The marketing of Pradaxa is subject to a risk management plan (RMP) including a “Patient safety information card”. The “Patient safety information card”, emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

Please provide patient safety information card (patient card) to each patient who is prescribed with Pradaxa. Explain to the patient the implications of anticoagulant treatment including the need for compliance. Please also explain the signs of bleeding and when to seek medical attention.

The patient card will inform physicians and dentists about the patient’s anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every health care provider.

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1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75

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”.

WARNING: DISCONTINUING PRADAXA IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE
Discontinuing Pradaxa places patients at an increased risk of thrombotic events.
If anticoagulation with Pradaxa must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant [see Special warnings and precautions for use (section 4.4)].

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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.

4.2 Posology and method of administration

Posology

Primary prevention of Venous Thromboembolism in Orthopaedic Surgery (VTE)

The recommended doses of dabigatran etexilate and the duration of therapy for primary prevention of venous thromboembolism(VTE) in orthopaedic surgery are shown in table 1.

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Table 1: Dose recommendations and duration of therapy for primary prevention of venous thromboembolism (VTE) in orthopaedic surgery

| | Treatment initiation on the day of surgery 1-4 hours after completed surgery | Maintenance dose starting on the first day after surgery | Duration of maintenance dose |
|---|---|--|--|
| Patients following elective knee replacement surgery | single capsule of 110 mg dabigatran etexilate | 220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg | 10 days |
| Patients following elective hip replacement surgery | | | 28-35 days |
| <i>Dose reduction recommended</i> | | | |
| Patients with moderate renal impairment (creatinine clearance (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).

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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. In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see 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 venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

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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
- 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

Increased risk of stroke with discontinuation of Pradaxa

Discontinuing Pradaxa in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If Pradaxa must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

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. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation

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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: Factors which may increase the haemorrhagic risk.

| | Risk factor |
|---|--|
| Pharmacodynamic and kinetic factors | Age \geq 75 years |
| Factors increasing dabigatran plasma levels | <p><u>Major:</u></p> <ul style="list-style-type: none"> • Moderate renal impairment in adult patients (30-50 mL/min CrCL) • Strong P-gp inhibitors (see section 4.3 and 4.5) • Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5) <p><u>Minor:</u></p> <ul style="list-style-type: none"> • Low body weight (<50 kg) in adult patients |
| Pharmacodynamic interactions (see section 4.5) | <ul style="list-style-type: none"> • ASA and other platelet aggregation inhibitors such as clopidogrel • NSAID • SSRIs or SNRIs • Other medicinal products which may impair haemostasis |
| Diseases / procedures with special haemorrhagic risks | <ul style="list-style-type: none"> • Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux |

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

Precautions and management of the haemorrhagic risk

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

Benefit-risk assessment

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs, see section 4.5), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. This is especially relevant in specific patient groups at risk, such as

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elderly (age > 75), patients with impaired renal function (CrCl 30-50ml/min), patients on concomitant use of P-gp inhibitors or a combination of the above. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Close clinical surveillance

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 2 above). Particular caution should be exercised when 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. Haemodialysis can remove dabigatran.

Use of proton-pump inhibitors

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

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 Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Table 3 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding (see section 5.1)

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

| Test (trough value) | Threshold |
|-------------------------------------|-------------------------|
| dTT [ng/mL] | >67 |
| ECT [x-fold upper limit of normal] | No data |
| aPTT [x-fold upper limit of normal] | >1.3 |
| INR | Should not be performed |

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

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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.

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

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

| Renal function (CrCL in mL/min) | Estimated half-life (hours) | Dabigatran etexilate should be stopped before elective surgery | |
|---------------------------------------|--------------------------------|--|-----------------------------|
| | | High risk of bleeding or major surgery | Standard risk |
| ≥80 | ~ 13 | 2 days before | 24 hours before |
| ≥50-<80 | ~ 15 | 2-3 days before | 1-2 days before |
| ≥30-<50 | ~ 18 | 4 days before | 2-3 days before (>48 hours) |

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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 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.

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.

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4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 5) is expected to result in increased dabigatran plasma concentrations.

If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. Dose reductions may be required in combination with some P-gp inhibitors (see sections 4.2, 4.3, 4.4 and 5.1).

Table 5: Transporter interactions

| | |
|--|---|
| <u>P-gp inhibitors</u> | |
| <i>Concomitant use contraindicated (see section 4.3)</i> | |
| Ketoconazole | 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. |
| Dronedaron | When dabigatran etexilate and dronedaron 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 dronedaron bid, and about 2.1-fold and 1.9-fold, respectively, after a single dose of 400 mg. |
| Itraconazole, cyclosporine | Based on <i>in vitro</i> results a similar effect as with ketoconazole may be expected. |
| Glecaprevir / pibrentasvir | 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. |
| <i>Concomitant use not recommended</i> | |
| Tacrolimus | 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. |
| <i>Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)</i> | |
| Verapamil | When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C _{max} and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2 and 4.4). The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the |

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| | <p>dabigatran etexilate intake (increase of C_{max} by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold and AUC by about 1.5-fold).</p> <p>There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.</p> |
| 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_{max} were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4). |
| Quinidine | Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3 rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4). |
| Clarithromycin | When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 1.19-fold and C_{max} by about 1.15-fold was observed. |
| Ticagrelor | <p>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_{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_{max} and AUC, respectively.</p> <p>Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by 1.49-fold and 1.65-fold, respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose.</p> <p>Concomitant administration of 90 mg ticagrelor b.i.d. (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.</p> |
| 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. |
| <u>P-gp inducers</u> | |

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| <i>Concomitant use should be avoided.</i> | |
| 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. |
| <i><u>Protease inhibitors such as ritonavir</u></i> | |
| <i>Concomitant use not recommended</i> | |
| 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. |
| <i><u>P-gp substrate</u></i> | |
| 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).

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).

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Table 6: Interactions with anticoagulants and antiplatelet aggregation medicinal products

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| NSAIDs | NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in 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. |
| Clopidogrel | In young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by about 30-40 % (see section 4.4) . |
| ASA | Co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively (see section 4.4). |
| LMWH | The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin. |

Other interactions

Table 7: Other interactions

| | |
|--|---|
| <i>Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</i> | |
| SSRIs, SNRIs | SSRIs and SNRIs increased the risk of bleeding in all treatment groups of a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY). |
| <i>Substances influencing gastric pH</i> | |
| Pantoprazole | 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. |
| Ranitidine | Ranitidine administration together with dabigatran etexilate had no clinically relevant effect on the extent of absorption of dabigatran. |

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Interactions linked to dabigatran etexilate and dabigatran metabolic profile

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There is limited amount of data from the use of Pradaxa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pradaxa should not be used during pregnancy unless clearly necessary.

Breast-feeding

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

Fertility

No human data available.

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

4.7 Effects on ability to drive and use machines

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.

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

Table 8: Adverse reactions

| SOC / Preferred term | Frequency |
|---|-----------|
| Blood and lymphatic system disorders | |
| Haemoglobin decreased | Common |
| Anaemia | Uncommon |
| Haematocrit decreased | Uncommon |
| Thrombocytopenia | Rare |
| Neutropenia | Not known |
| Agranulocytosis | Not known |
| Immune system disorder | |
| Drug hypersensitivity | Uncommon |
| Anaphylactic reaction | Rare |
| Angioedema | Rare |
| Urticaria | Rare |
| Rash | Rare |
| Pruritus | Rare |
| Bronchospasm | Not known |
| Nervous system disorders | |
| Intracranial haemorrhage | Rare |
| Vascular disorders | |
| Haematoma | Uncommon |
| Wound haemorrhage | Uncommon |
| Haemorrhage | Rare |
| Respiratory, thoracic and mediastinal disorders | |
| Epistaxis | Uncommon |
| Haemoptysis | Rare |
| Gastrointestinal disorders | |
| Gastrointestinal haemorrhage | Uncommon |
| Rectal haemorrhage | Uncommon |
| Haemorrhoidal haemorrhage | Uncommon |
| Diarrhoea | Uncommon |

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|---|-----------|
| Nausea | Uncommon |
| Vomiting | Uncommon |
| Gastrointestinal ulcer, including oesophageal ulcer | Rare |
| Gastroesophagitis | Rare |
| Gastroesophageal reflux disease | Rare |
| Abdominal pain | Rare |
| Dyspepsia | Rare |
| Dysphagia | Rare |
| Hepatobiliary disorders | |
| Hepatic function abnormal/ Liver function Test abnormal | Common |
| Alanine aminotransferase increased | Uncommon |
| Aspartate aminotransferase increased | Uncommon |
| Hepatic enzyme increased | Uncommon |
| Hyperbilirubinaemia | Uncommon |
| Skin and subcutaneous tissue disorder | |
| Skin haemorrhage | Uncommon |
| Alopecia | Not known |
| Musculoskeletal and connective tissue disorders | |
| Haemarthrosis | Uncommon |
| Renal and urinary disorders | |
| Genitourological haemorrhage, including haematuria | Uncommon |
| General disorders and administration site conditions | |
| Injection site haemorrhage | Rare |
| Catheter site haemorrhage | Rare |
| Bloody discharge | Rare |
| Injury, poisoning and procedural complications | |
| Traumatic haemorrhage | Uncommon |
| Post procedural haematoma | Uncommon |
| Post procedural haemorrhage | Uncommon |
| Post procedural discharge | Uncommon |
| Wound secretion | Uncommon |
| Incision site haemorrhage | Rare |
| Anaemia postoperative | Rare |
| Surgical and medical procedures | |
| Wound drainage | Rare |
| Post procedural drainage | Rare |

Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of 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

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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 9 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 9: Number (%) of patients experiencing the adverse reaction bleeding

| | Dabigatran etexilate 150 mg N (%) | Dabigatran etexilate 220 mg N (%) | Enoxaparin N (%) |
|----------------|---|---|---------------------|
| Treated | 1,866(100.0) | 1,825(100.0) | 1,848(100.0) |
| Major bleeding | 24 (1.3) | 33 (1.8) | 27 (1.5) |
| Any bleeding | 258(13.8) | 251(13.8) | 247(13.4) |

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.

Reporting of suspected adverse reactions

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:

<https://sideeffects.health.gov.il>

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

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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. (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.

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Pharmacodynamic effects

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

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

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

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

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

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

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.

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Clinical efficacy and safety

Ethnic origin

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

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

In 2 large 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 10). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 10).

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

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

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

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

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

Data for adjudicated major bleeding endpoints are shown in table 12 below.

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Table 10: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

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

Table 11: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

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

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

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

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).

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_{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_{max} and AUC were dose proportional.

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The oral bioavailability may be increased by 75 % after a single dose and 37 % at steady state compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (HPMC) capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate (see section 4.2).

Distribution

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

Biotransformation

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabeled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85 %). Faecal excretion accounted for 6 % of the administered dose. Recovery of the total radioactivity ranged from 88-94 % of the administered dose by 168 hours post dose. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

Elimination

Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. Half-life is prolonged if renal function is impaired as shown in table 13.

Special populations

Renal insufficiency

In phase I studies the exposure (AUC) of dabigatran after the oral administration of 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).

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Table 13: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function.

| glomerular filtration rate (CrCL, [mL/min]) | gMean (gCV%; range) half-life [h] |
|---|---|
| ≥80 | 13.4 (25.7 %; 11.0-21.6) |
| ≥50-<80 | 15.3 (42.7 %; 11.7-34.1) |
| ≥30-<50 | 18.4 (18.5 %; 13.3-23.0) |
| <30 | 27.2(15.3 %; 21.6-35.0) |

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_{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.

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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, hydroxypropylcellulose, talc acacia, hypromellose, dimeticone,

Capsule shell: HPMC capsule size 2 (imprinted with Black Ink): Hypromellose, Titanium dioxide, Water, purified, Potassium chloride, Carrageenan

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25°C in the original package

6.5 Nature and contents of container

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

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 hardcapsules should not be pushed through the blister foil.
- The blister foil should only be peeled off, when a hard capsule is required.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Israel Ltd., Medinat Ha'Yehudim St 89, B.O.X 4124, 4676672 Hertzliya Pituach

8. MARKETING AUTHORISATION NUMBER(S)

Pradaxa 75 mg capsules Reg. no. 142 95 32973 00/01/02

9. MANUFACTURER

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

This leaflet was revised in January 2022 according to MOH's guidelines.