This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in 07.2019 and updated according to the MoH guideline in July 2019

PRADAXA

Dabigatran Etexilate 150 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.

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

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)].

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF).

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

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism in adult patients with NVAF (SPAF)
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)

The recommended doses of Pradaxa in the indications SPAF, DVT and PE are shown in table 1.

Table 1: Dose recommendations for SPAF, DVT and PE

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

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

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

Assessment of renal function prior to and during Pradaxa treatment

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

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

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

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

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

Duration of use

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

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

Indication	**Duration of use**
SPAF	Therapy should be continued long term.
DVT/PE	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.

Missed dose

A forgotten Pradaxa dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.
No double dose should be taken to make up for missed individual doses.

Discontinuation of Pradaxa

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

Switching

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

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

Pradaxa treatment to Vitamin K antagonists (VKA):
The starting time of the VKA should be adjusted based on CrCL as follows:

- CrCL ≥ 50 mL/min, VKA should be started 3 days before discontinuing Pradaxa
- CrCL ≥ 30-< 50 mL/min, VKA should be started 2 days before discontinuing Pradaxa

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

VKA to Pradaxa:

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

Cardioversion (SPAF)

Patients can stay on Pradaxa while being cardioverted.

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

Percutaneous coronary intervention (PCI) with stenting (SPAF)

Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with Pradaxa 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 Pradaxa in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated (see section 4.3).

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

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

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

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

Weight

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

Gender

No dose adjustment is necessary (see section 5.2).

Paediatric population

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

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

Method of administration
Pradaxa is for oral use.
The capsules can be taken with or without food. Pradaxa should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach.
Patients should be instructed not to open the capsule as this may increase the risk of bleeding (see sections 5.2 and 6.6).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 mL/min)
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances. 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 and dronedarone (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

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

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

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

Risk factors

Table 3 summarises factors which may increase the haemorrhagic risk.

Table 3: Factors which may increase the haemorrhagic risk.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (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) Minor: • Low body weight (< 50 kg)

Pharmacodynamic interactions (see section 4.5)	• 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	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

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

Precautions and management of the haemorrhagic risk

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

Benefit-risk assessment

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

Close clinical surveillance

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

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

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

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

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

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

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

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

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

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

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

Surgery and interventions

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

Patients can stay on Pradaxa while being cardioverted. Pradaxa treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see section 4.2).
Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer (see section 5.2). This should be considered in advance of any procedures. In such cases a coagulation test (see sections 4.4 and 5.1) may help to determine whether haemostasis is still impaired.

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

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

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

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

Table 5 summarises discontinuation rules before invasive or surgical procedures.

Table 5: Discontinuation rules before invasive or surgical procedures

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Pradaxa 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)

Spinal anaesthesia/epidural anaesthesia/lumbar puncture

Procedures such as spinal anaesthesia may require complete haemostatic function.

The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of Pradaxa. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Postoperative phase

Pradaxa 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 moderate renal impairment (CrCL 30-50 mL/min), should be treated with caution (see sections 4.4 and 5.1).

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

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

Hepatic impairment

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

Interaction with P-gp inducers

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

Myocardial Infarction (MI)

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

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

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

Active Cancer Patients (DVT/PE)

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 6) is expected to result in increased dabigatran plasma concentrations.

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

Table 6: Transporter interactions

P-gp inhibitors	
Concomitant use contraindicated (see section 4.3)	
Ketoconazole	Ketoconazole increased total dabigatran $AUC_{0-\infty}$ 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.
Dronedarone	When dabigatran etexilate and dronedarone were given at the same time total dabigatran $AUC_{0-\infty}$ 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.
Itraconazole, cyclosporine	Based on *in vitro* results a similar effect as with ketoconazole may be expected.
Concomitant use not recommended	
Tacrolimus	Tacrolimus has been found *in vitro* to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors.
Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)	
Verapamil	When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2

	and 4.4). The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of C_{max} by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold and AUC by about 1.5-fold). There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.
Amiodarone	When Pradaxa was co-administered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).
Quinidine	Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ 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	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. Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg

	dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by 1.49-fold and 1.65-fold, respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor b.i.d. (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.
Posaconazole	Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.
<u>*P-gp inducers*</u>	
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.
<u>*Protease inhibitors such as ritonavir*</u>	
Concomitant use not recommended	
e.g. ritonavir and its combinations with other protease	These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with Pradaxa.

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

Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and 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 7: Interactions with anticoagulants and antiplatelet aggregation medicinal products

NSAIDs	NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin.
Clopidogrel	In young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ 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 8: Other interactions

Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)	
SSRIs, SNRIs	SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups,
Substances influencing gastric pH	
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 Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Pradaxa should not be used during pregnancy unless clearly necessary.

Breast-feeding

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

Fertility

No human data available.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Table 9: Number of patients studied, maximum daily dose in phase III studies

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

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

The most commonly reported events are bleedings occurring in approximately 16.6 % in patients with atrial fibrillation treated long-term for the prevention of stroke and systemic embolism and in 14,4 % of patients treated for DVT/PE. Furthermore, bleedings occurred in 19.4 % of patients in the DVT/PE prevention trial RE-MEDY and in 10.5 % of patients in the DVT/PE prevention trial RE-SONATE.

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

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

Tabulated list of adverse reactions

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

Table 10: Adverse reactions

	Frequency	
SOC / Preferred term.	Stroke and systemic embolism prevention in patients with atrial fibrillation	DVT/PE treatment and DVT/PE prevention
Blood and lymphatic system disorders		
Anaemia	Common	Uncommon
Haemoglobin decreased	Uncommon	Not known
Thrombocytopenia	Uncommon	Rare
Haematocrit decreased	Rare	Not known
Immune system disorder		
Drug hypersensitivity	Uncommon	Uncommon
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon
Anaphylactic reaction	Rare	Rare
Angioedema	Rare	Rare
Urticaria	Rare	Rare
Bronchospasm	Not known	Not known
Nervous system disorders		
Intracranial haemorrhage	Uncommon	Rare
Vascular disorders		
Haematoma	Uncommon	Uncommon
Haemorrhage	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Gastrointestinal disorders		
Gastrointestinal haemorrhage	Common	Common
Abdominal pain	Common	Uncommon
Diarrhoea	Common	Uncommon
Dyspepsia	Common	Common
Nausea	Common	Uncommon
Rectal haemorrhage	Uncommon	Common
Haemorrhoidal haemorrhage	Uncommon	Uncommon
Gastrointestinal 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
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 Pradaxa may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term Pradaxa treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion

have been reported for Pradaxa. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. A specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (SPAF)

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

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

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

Subjects randomized to Pradaxa 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin [$p < 0.05$]. Both dose strengths of Pradaxa had also a statistically significant lower total bleed rate. Subjects randomized to 110 mg Pradaxa twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomized to 150 mg Pradaxa twice daily had a significantly higher risk for major GI bleeds compared with warfarin (hazard ratio 1.48 [p=0.0005]. This effect was seen primarily in patients $\geq$ 75 years.
The clinical benefit of dabigatran with regard to stroke and systemic embolism prevention and decreased risk of ICH compared to warfarin is preserved across individual subgroups, e.g. renal impairment, age, concomitant medicinal product use such as anti-platelets or P-gp inhibitors. While certain patient subgroups are at an increased risk of major bleeding when treated with an anticoagulant, the excess bleeding risk for dabigatran is due to GI bleeding, typically seen within the first 3-6 months following initiation of Pradaxa therapy.

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

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

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

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

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

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

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

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

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

Table 14 shows bleeding events in pivotal study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The rate of the combination of MBEs/CRBEs and the rate of any bleeding was significantly lower at a nominal alpha level of 5 % in patients receiving placebo as compared with those receiving dabigatran etexilate.

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

	Pradaxa150 mg twice daily	Placebo	Hazard ratio vs placebo (95% confidence interval)
Treated patients	684	659	
Major bleeding events	2 (0.3 %)	0	Not calculable*
Intracranial bleeding	0	0	Not calculable*
Major GI bleeding	2 (0.3%)	0	Not calculable*
Life-threatening	0	0	Not

bleeds			calculable*
Major bleeding event/clinical relevant bleeds	36 (5.3 %)	13 (2.0 %)	2.69 (1.43, 5.07)
Any bleeding	72 (10.5 %)	40 (6.1 %)	1.77 (1.20, 2.61)
Any GI bleeds	5 (0.7%)	2 (0.3%)	2.38 (0.46, 12.27)

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il).

4.9 Overdose

Pradaxa doses beyond those recommended, expose the patient to increased risk of bleeding.

In case of an overdose suspicion, coagulation tests can help to determine a bleeding risk (see sections 4.4 and 5.1). A calibrated quantitative (dTT) test or repetitive dTT measurements allow prediction of the time by when certain dabigatran levels will be reached (see section 5.1), also in case additional measures e.g. dialysis have been initiated.

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

Management of bleeding complications

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.
Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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

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

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

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

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

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

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

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

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

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

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

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

<u>Clinical efficacy and safety</u>

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

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

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

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

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

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

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

% refers to yearly event rate

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

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

% refers to yearly event rate

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

	Pradaxa 110 mg twice daily	Pradaxa 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
All-cause mortality			
Incidences (%)	446 (3.75)	438 (3.64)	487 (4.13)
Hazard ratio vs. warfarin (95 % CI)	0.91 (0.80, 1.03)	0.88 (0.77, 1.00)	
p-value	0.1308	0.0517	
Vascular mortality			

Incidences (%)	289 (2.43)	274 (2.28)	317 (2.69)
Hazard ratio vs. warfarin (95 % CI)	0.90 (0.77, 1.06)	0.85 (0.72, 0.99)	
p-value	0.2081	0.0430	

% refers to yearly event rate

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

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

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

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

For the primary safety endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with dabigatran compared to warfarin increased with age. Relative risk was highest in patients ≥ 75 years. The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran etexilate and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and $CHADS_2$ score.

Table 19: Hazard Ratio and 95 % CI for major bleeds by subgroups

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

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 $CHADS_2$ 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 statistically significant 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 significant 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, randomized, open-label, multicenter, exploratory study with blinded, centrally adjudicated endpoint evaluation (RE-CIRCUIT) was conducted in 704 patients who were under stable anticoagulant treatment. The study compared 150 mg twice daily uninterrupted dabigatran etexilate with uninterrupted INR-adjusted warfarin in catheter ablation of paroxysmal or persistent atrial fibrillation. Of the 704 enrolled patients, 317 underwent atrial fibrillation ablation on uninterrupted dabigatran and 318 underwent atrial fibrillation ablation on uninterrupted warfarin. All patients underwent a Trans-oesophageal Echocardiography (TEE) prior to catheter ablation. The primary outcome (adjudicated major bleeding according to ISTH criteria) occurred in 5 (1.6 %) patients in the dabigatran etexilate group and 22 (6.9 %) patients in the warfarin group (risk difference −5.3%; 95% CI −8.4, −2.2; P=0.0009). There was no stroke/systemic embolism/TIA (composite) event in the dabigatran etexilate arm, and one event (TIA) in the warfarin arm from the time of ablation and until 8 weeks post-ablation. This exploratory study showed that dabigatran etexilate was associated with a significant reduction in MBE rate compared with INR-adjusted warfarin in the setting of ablation.

Patients who underwent Percutaneous coronary intervention (PCI) with stenting

A prospective, randomized, 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 aspirin was conducted in 2725 patients with non valvular atrial fibrillation who underwent a PCI with stenting (RE-DUAL PCI). Patients were randomized 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 deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE treatment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population

The pharmacokinetics and pharmacodynamics of dabigatran etexilate administered twice daily for three consecutive days (total 6 doses) at the end of standard anticoagulant therapy were assessed in an open-label safety and tolerability study in 9 stable adolescents (12 to < 18 years). All patients received an initial oral dose of 1.71 (± 10%) mg/kg of dabigatran etexilate (80 % of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on dabigatran concentrations and clinical assessment, the dose was subsequently modified to a target dose of 2.14 (± 10 %) mg/kg of dabigatran etexilate (100 % of the adult dose adjusted for

the patient's weight). In this small number of adolescents, dabigatran etexilate capsules were apparently tolerated with only three mild and transient gastrointestinal adverse events reported by two patients. According to the relatively low exposure, coagulation at 72 hrs (presumed dabigatran trough level at steady state or close to steady state conditions) was only slightly prolonged with aPTT at maximum 1.60 fold, ECT 1.86 fold, and Hemoclot® TT (Anti-FIIa) 1.36 fold, respectively. Dabigatran plasma concentrations observed at 72 hrs were relatively low, between 32.9 ng/mL and 97.2 ng/mL at final doses between 100 mg and 150 mg (gMean dose normalized total dabigatran plasma concentration of 0.493 ng/mL/mg).

5.2 Pharmacokinetic properties

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration of Pradaxa was approximately 6.5 %.
After oral administration of Pradaxa in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with C_{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_{max} and AUC were dose proportional.

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

Distribution

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

Biotransformation

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

Elimination

Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. Half-life is prolonged if renal function is impaired as shown in table 23.

Special populations

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

In a small number of volunteers with severe renal insufficiency (CrCL 10-30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.2, 4.3 and 4.4).

Table 23: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function.

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

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

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

The median CrCL in the RE-COVER study was 100.4 mL/min. 21.7 % of patients had mild renal impairment (CrCL > 50 - < 80 mL/min) and 4.5% of patients had a moderate renal impairment (CrCL between 30 and 50 mL/min). Patients with mild and moderate renal impairment had at steady state an average 1.8-fold and 3.6-fold higher pre-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_{max} compared to young subjects.
The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31 % higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects between 65 and 75 years (see sections 4.2 and 4.4).

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

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

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

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

Pharmacokinetic interactions

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects observed in the repeated-dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran.

An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5- to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

In lifetime toxicology studies in rats and mice, there was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: tartaric acid, acacia, hypromellose, dimeticone, talc, hydroxypropylcellulose

Capsule shell: carrageenan, potassium chloride, titanium dioxide, indigo carmine (E132), hypromellose, purified water, and black printing ink.

6.2 Incompatibilities

Not applicable.

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 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.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Israel Ltd., #89 Medinat Ha'Yehudim St., Hertzliya Pituach 4676672

8. MARKETING AUTHORISATION NUMBER(S)

Pradaxa 150 mg capsules Reg. no. 145 63 33359 00/01/02

9. MANUFACTURER

Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany

The format of this leaflet was approved by the Ministry of Health on July 2019 and updated according to the guidelines of the Ministry of Health in July 2019.