Pradaxa® 75 mg hard capsules

Pradaxa® 110 mg hard capsules

Boehringer Ingelheim

Composition
Pradaxa 75 mg, hard capsules:
Each hard capsule contains 75 mg of dabigatran etexilate (as mesilate)

Pradaxa 110 mg, hard capsules
Each hard capsule contains 110 mg of dabigatran etexilate (as mesilate)

Excipients: Capsule fill: Tartaric acid, Acacia, Hypromellose, Dimeticone 350, Talc, Hydroxypropylcellulose
Capsule shell: Carrageenan, Potassium Chloride, Titanium Dioxide, Indigo Carmine (E132), Sunset Yellow (E110), Hypromellose, Water purified
Black printing ink: Shellac, N-Butyl alcohol, Isopropyl alcohol, Industrial methylated spirit, Iron oxide black (E172), Purified water, Propylene glycol

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: oral direct thrombin inhibitor

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

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

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect.
An aPTT greater than 2.5 times control is suggestive of excess anticoagulation.

Steady state (after day 3) dabigatran peak plasma concentration, measured 2 – 4 hours after 220 mg dabigatran etexilate administration, is expected to be around 270 ng/ml, with an expected range of 80 – 460 ng/ml. The dabigatran through concentration, measured at the end of the dosing interval (24 hours after the last 220 mg dabigatran dose), is expected to be around 40 ng/ml, with expected range of 10 – 90 ng/ml.

Ethnic origin:
More than 99% of efficacy and safety data were generated in Caucasians.

Clinical trials in VTE prophylaxis following major joint replacement surgery:
In 2 large randomized, parallel group, double-blind, dose-confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received 75 mg or 110 mg within 1 – 4 hours of surgery followed by 150 mg or 220 mg daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and daily thereafter.
In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.
The results of the knee study (RE-MODEL) with respect to the primary end-point, total including asymptomatic venous thromboembolism (VTE) plus all-cause mortality showed that the antithrombotic effect of both doses of Pradaxa were statistically non-inferior to that of enoxaparin.
Similarly Pradaxa, total including asymptomatic VTE and all-cause mortality constituted the primary end-point for the hip study (RE-NOVATE). Again Pradaxa at both daily doses was statistically non-inferior to enoxaparin 40 mg daily.
Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are

Special populations

Renal insufficiency:
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 Dosage and Administration, Contraindications, Special Warnings & Precautions).

Elderly patients:
Specific pharmacokinetic 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. Population-based pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran after repeated doses in patients (up to 88 years). The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance (see sections Dosage and Administration, Special Warnings & Precautions).

Hepatic insufficiency:
No change in dabigatran exposure was seen in 12 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls (see sections Dosage and Administration, Special Warnings & Precautions).

Body weight:
Population pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran in patients of 48 to 120 kg body weight. Body weight had a minor effect on the plasma clearance of dabigatran resulting in higher exposure in patients with low body weight (see sections Dosage and Administration, Special Warnings & Precautions).

Gender:
Active substance exposure in female patients is about 40% to 50% higher than in male patients and no dose adjustment is recommended. There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women. (See sections Dosage and Administration, Special Warnings & Precautions).

Ethnic origin:
The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. No pharmacokinetic data in black patients are available.

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-glycoprotein transporter interaction) and diclofenac (CYP2C9).
Dabigatran exposure in healthy subjects was increased by 60% in the presence of amiodarone.

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

Dosage and Administration
Pradaxa should be taken with water, with or without food.

Adults:

Prevention of Venous Thromboembolism (VTE) in patients following knee replacement surgery:
The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment with Pradaxa should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Prevention of Venous Thromboembolism (VTE) in patients following hip replacement surgery:
The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment with Pradaxa should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28 – 35 days.

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

Special patient populations:

Renal impairment:
Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance < 30 ml/min)

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in tables 1 and 2 below.

Table 1: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopeadic 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 differences vs. enoxaparin (%)	−0.8	0.4	
95% CI	−2.5, 0.8	−1.5, 2.2	
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 differences vs. enoxaparin (%)	−1.0	0.3	
95% CI	−3.1, 1.2	−2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	

Table 2: 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	1146	1163	1154
Number of MBE N (%)	23 (2.0)	15 (1.3)	18 (1.8)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N (%)	10 (1.5)	9 (1.3)	9 (1.3)

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.

Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated (see section Contraindications).

In patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections Special warnings and precautions for use and Pharmacodynamic properties).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28 – 35 days.

Elderly:
In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections Special warnings and precautions for use and Pharmacodynamic properties).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28 – 35 days.

Hepatic impairment:
Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials. Therefore the use of Pradaxa is not recommended in this population (see sections Special warnings and precautions for use and Pharmacokinetic properties). ALT should be measured as part of the standard pre-operative evaluation (see section Special warnings and precautions for use).

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 Pharmacokinetic properties) but close clinical surveillance is recommended (see section Special warnings and precautions for use).

Post-surgical patients with an increased risk for bleeding:
Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min), should be treated with caution (see sections Special warnings and precautions for use and Pharmacokinetic properties)

Children and adolescents:
There is no experience in children and adolescents.
Pradaxa is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of Pradaxa with Amiodarone:
Dosing should be reduced to 150 mg Pradaxa daily in patients who received concomitantly dabigatran etexilate and amiodarone (see section Interactions).

Switching from Pradaxa treatment to parenteral anticoagulant:
Wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant (see section Interactions).

Switching from parenteral anticoagulants treatment to Pradaxa:
No data are available, therefore it is not recommended to start the administration of Pradaxa before the next scheduled dose of the parenteral anticoagulant would have been due (see section Interactions).

Contraindications

- Hypersensitivity to the active substance, its ester or salt or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with quinidine (see section Interactions)

Special Warnings and Precautions

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 anesthesia, gastrointestinal paresis, and surgical effects independent of the oral drug 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 drug administration. Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

Distribution
Low (34 – 35 %) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigtran of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.
C_{max} and the area under the plasma concentration-time curve were dose proportional. Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12 – 14 hours in healthy volunteers and 14 – 17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose.

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

- Hypersensitivity to the active substance, its ester or salt or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with quinidine (see section Interactions)

Special Warnings and Precautions
Hepatic impairment:
Patients with elevated liver enzymes > 2 ULN were excluded in controlled clinical trials. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation.

Haemorrhagic risk:
Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially in the following situations that may increase the hemorrhagic risk: diseases associated with an increased risk of bleeding, such as congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, recent biopsy or major trauma, recent intracranial haemorrhage or brain, spinal or ophthalmic surgery, bacterial endocarditis.

In general, in patients > 75 years, patients with body weight < 50 kg, patients with renal impairment, there is an increased risk of bleeding on anticoagulation. Patients with renal impairment and the elderly have increased drug exposure of dabigatran (see section Pharmacokinetics). Limited data is available in patients < 50 kg. Therefore Pradaxa should be used with caution and a close clinical surveillance (looking for signs of bleeding or anemia) is required throughout the treatment period.
The 150 mg daily dose is intended for patients with moderate renal impairment (50 – 30 ml/min).

When severe bleedings occur treatment must be discontinued and the source of bleeding investigated (see section Overdose). An aPTT greater than 2.5 times control is suggestive of excess anticoagulation.

Agents that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Pradaxa (see section Interactions).

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events:
There are limited efficacy and safety data for dabigatran available in these patients and therefore they should be treated with caution.

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture:
In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of dabigatran and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with postoperative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.

Therefore the use of Pradaxa is not recommended in patients undergoing anaesthesia with post-operative indwelling epidural catheters.

Administration of the first dose of Pradaxa should occur a minimum of two hours after the catheter is removed. These patients require frequent observation for neurological signs and symptoms.

Hip fracture surgery:
There is no data on the use of Pradaxa in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

Colorants:
Pradaxa hard capsules contain the colorant sunset yellow (E110), which may cause allergic reactions.

Interactions:
Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents:
The following treatments are not recommended concomitantly with Pradaxa: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see sections Dosage and Administration and Special Warnings and Precautions).

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 drug-drug interactions are not expected with Pradaxa or dabigatran.

Atorvastatin: When Pradaxa was coadministered with atorvastatin, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were unchanged indicating a lack of interaction.

NSAIDs: When Pradaxa was coadministered with diclofenac, the plasma exposure of both drugs remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives >12 hours, close observation for signs of bleeding is recommended (see section Special Warnings and Precautions).

Transporter interactions:
Amiodarone: Amiodarone is an inhibitor of the efflux transporter P-glycoprotein and dabigatran etexilate a substrate of this transporter. When Pradaxa was coadministered with 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 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Dosing should be reduced to 150 mg Pradaxa daily in patients who received concomitantly dabigatran etexilate and amiodarone (see section Dosage and Administration).

P- glycoprotein inhibitors:
Caution should be exercised with strong P- glycoprotein inhibitors like verapamil, clarithromycin, and others. The P- glycoprotein inhibitor quinidine is contraindicated (see section Contraindications).

P- glycoprotein inducers:
Potent P- glycoprotein inducers such as rifampicin or St John's wort (Hypericum perforatum), may reduce the systemic exposure of dabigatran. Caution is advised when co-administering these medicinal products.

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

Gastric pH:
Pantoprazole: When Pradaxa was coadministered with pantoprazole, a decrease in dabigatran area under the plasma concentration - time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with Pradaxa in clinical trials and no effects on bleeding or efficacy were observed.

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

Pregnancy and lactation:
Pregnancy:
There are no adequate data from the use of Pradaxa in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
The increased bleeding risk with Pradaxa may constitute a risk in treatment during pregnancy.
Women of child-bearing potential should avoid pregnancy during treatment with Pradaxa.
Pradaxa should not be used during pregnancy unless clearly necessary.

SOC/Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Number of patients treated	2737 (100)	2682 (100)	3108 (100)
Hepatobiliary disorders			
	Uncommon		
Alaninine aminotransferase increased	18 (0.7)	7 (0.3)	28 (0.9)
Aspartate aminotransferase increased	9 (0.3)	5 (0.2)	15 (0.5)
Hepatic function abnormal/ Liver function Test abnormal	6 (0.2)	10 (0.4)	7 (0.2)
Hepatic enzyme increased	4 (0.2)	5 (0.2)	11 (0.4)
Hyperbilirubinaemia	4 (0.1)	3 (0.1)	4 (0.1)
Transaminases increased	0 (0.0)	2 (0.1)	1 (0.0)
Skin and subcutaneous tissue disorder			
	Common		
Skin haemorrhage	45 (1.6)	57 (2.1)	61 (2.0)
Musculoskeletal and connective tissue and bone disorders			
	Uncommon		
Haemarthrosis	9 (0.3)	7 (0.3)	17 (0.6)
Renal and urinary disorders			
	Common		
Haematuria	38 (1.4)	33 (1.4)	25 (0.8)
General disorders and administration site conditions			
	Uncommon		
Injection site haemorrhage	21 (0.8)	19 (0.7)	27 (0.9)
Bloody discharge	2 (0.1)	6 (0.2)	6 (0.2)
Catheter site haemorrhage	2 (0.1)	1 (0.0)	7 (0.2)
Investigations			
	Common		
Haemoglobin decreased	45 (1.6)	35 (1.3)	74 (2.4)
	Uncommon		
Haematocrit decreased	0 (0.0)	6 (0.2)	4 (0.1)
Injury, poisoning and procedural complications			
	Common		
Wound secretion	130 (4.8)	130 (4.9)	93 (3.0)
Anaemia postoperative	99 (3.6)	87 (3.2)	120 (3.7)
Post procedural haematoma	66 (2.4)	45 (1.7)	78 (2.5)
Post procedural haemorrhage	37 (1.4)	54 (2.0)	56 (1.8)

Pradaxa should not be used during pregnancy unless clearly necessary.

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

Effects on ability to drive and use machines:
No studies on the effects on the ability to drive and use machines have been performed.

Side Effects
A total of 10.084 patients were treated in 4 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 5419 were treated with 150 mg or 220 mg daily of Pradaxa, while 389 received doses less than 150 mg daily and 1168 received doses in excess of 220 mg daily.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

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

The table 3 shows the number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

Table 3 Bleeding events broken down to major and any bleeding in the pivotal hip and knee study.

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Treated	1866 (100.0)	1825 (100.0)	1848 (100.0)
Major Bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258 (13.8)	251 (13.8)	247 (13.4)

Table 4 shows the adverse reactions ranked under headings of SOC and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (< 1/10,000).

SOC/Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Number of patients treated	2737 (100)	2682 (100)	3108 (100)
Blood and lymphatic system disorders			
	Common		
Anaemia	110 (4.0)	117 (4.4)	141 (4.5)
	Uncommon		
Thrombocytopenia	5 (0.2)	2 (0.1)	5 (0.2)
Vascular disorders			
	Common		
Haematoma	38 (1.4)	37 (1.4)	55 (1.8)
Traumatic haematoma	37 (1.4)	41 (1.5)	51 (1.6)
Wound haemorhhage	35 (1.3)	28 (1.0)	31 (1.0)
	Uncommon		
Haemorrhage	5 (0.2)	18 (0.7)	21 (0.7)
Respiratory and thoracic system disorders			
	Uncommon		
Epistaxis	19 (0.7)	15 (0.6)	13 (0.4)
Gastrointestinal disorders			
	Common		
Gastrointestinal haemorrhage	33 (1.2)	17 (0.6)	20 (0.6)
Post procedural discharge	31 (1.1)	34 (1.3)	31 (1.0)
Surgical and medial procedures			
	Uncommon		
Post procedural drainage	11 (0.4)	13 (0.5)	16 (0.5)
Wound drainage	1 (0.0)	4 (0.2)	2 (0.1)

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Beyond the reported ALT findings the following laboratory chemistry data had been measured in phase 3 studies as presented in table 5.

Table 5: ALT findings the following laboratory chemistry

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Total rates of Alaninine aminotransferase increased 3 x ULN	68 (2.5)	58 (2.2)	95 (3.5)

Overdose
There is no antidote to Pradaxa or dabigatran. Doses of Pradaxa beyond those recommended expose the patient to increased risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

Dabigatran can be dialysed; there is no clinical experience to demonstrate the utility of this approach in clinical studies.

Storage conditions
Store below 30 °C.
Store in the original package in order to protect from moisture
Keep out of reach of children.

Nature and contents of container:
Aluminium blister strips.
Cartons containing 3, or 6 blister strips (30 x 1 or 60 x 1 hard capsules).

Special precautions for disposal and other handling:
When taking Pradaxa capsules out of the blister pack, please observe the following instructions:

- Take the Pradaxa hard capsules by peeling off the backing foil of the blister card.
- Do not push the Pradaxa hard capsules through the blister foil.
- Do not peel off the blister foil until a Pradaxa hard capsule is required.

Date of package insert: March 2008

Manufacturer:
Boehringer Ingelheim Pharma GmbH & Co. KG
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

70837-02

This is a medicament
Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament
The doctors and the pharmacist are experts in medicine, its benefits and risks.
Do not by yourself interrupt the period of treatment prescribed for you.
Do not repeat the same prescription without consulting your doctor.
Keep medicament out of reach of children!
Council of Arab Health Ministers – Union of Arab Pharmacists

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SOC/Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
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	Uncommon		
Thrombocytopenia	5 (0.2)	2 (0.1)	5 (0.2)
Vascular disorders			
	Common		
Haematoma	38 (1.4)	37 (1.4)	55 (1.8)
Traumatic haematoma	37 (1.4)	41 (1.5)	51 (1.6)
Wound haemorhhage	35 (1.3)	28 (1.0)	31 (1.0)
	Uncommon		
Haemorrhage	5 (0.2)	18 (0.7)	21 (0.7)
Respiratory and thoracic system disorders			
	Uncommon		
Epistaxis	19 (0.7)	15 (0.6)	13 (0.4)
Gastrointestinal disorders			
	Common		
Gastrointestinal haemorrhage	33 (1.2)	17 (0.6)	20 (0.6)
	Uncommon		
Rectal haemorrhage	12 (0.4)	15 (0.6)	5 (0.2)
Haemorrhoidal haemorrhage	4 (0.2)	8 (0.3)	2 (0.1)

Storage conditions
Store below 30 °C.
Store in the original package in order to protect from moisture
Keep out of reach of children.

Nature and contents of container:
Aluminium blister strips.
Cartons containing 3, or 6 blister strips (30 x 1 or 60 x 1 hard capsules).

Special precautions for disposal and other handling:
When taking Pradaxa capsules out of the blister pack, please observe the following instructions:

- Take the Pradaxa hard capsules by peeling off the backing foil of the blister card.
- Do not push the Pradaxa hard capsules through the blister foil.
- Do not peel off the blister foil until a Pradaxa hard capsule is required.

Date of package insert: March 2008

Manufacturer:
Boehringer Ingelheim Pharma GmbH & Co. KG
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

70837-02

This is a medicament
Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament
The doctors and the pharmacist are experts in medicine, its benefits and risks.
Do not by yourself interrupt the period of treatment prescribed for you.
Do not repeat the same prescription without consulting your doctor.
Keep medicament out of reach of children!
Council of Arab Health Ministers – Union of Arab Pharmacists

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