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 4.5).

Pradaxa should be swallowed as a whole with water, with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance 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 4.5)

4.4 Special warnings and precautions for use

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.

Patients with moderate renal impairment have an increased exposure to dabigatran. Limited data is available in patients < 50 kg and the elderly (see sections 4.2 and 5.2). In these situations, Pradaxa should be used with caution and a close clinical surveillance (looking for signs of bleeding or anemia) is required throughout the treatment period (see section 4.2).

When severe bleedings occur treatment must be discontinued and the source of bleeding investigated (see section 4.9).

Agents that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Pradaxa (see section 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 4.2 and 4.4).

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.

NSAIDs: When Pradaxa was coadministered with diclofenac, the plasma exposure of both medicinal products 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 4.4).

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 4.2).

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 4.3).

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 the 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.

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate 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.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate.
Pradaxa should not be used during pregnancy unless clearly necessary.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable 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 %.

The table 1 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 1 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 2 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)
	Uncommon		
Rectal haemorrhage	12 (0.4)	15 (0.6)	5 (0.2)
Haemorrhoidal haemorrhage	4 (0.2)	8 (0.3)	2 (0.1)
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)

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
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)
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)

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

Table 3: 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)

4.9 Overdose

There is no antidote to dabigatran. Doses of dabigatran etexilate 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombine inhibitors, ATC code: B01AE07

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 based on phase II studies.

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 trough 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 Venous Thromboembolism (VTE) prophylaxis following major joint replacement surgery:

In 2 large randomized, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received Pradaxa 75 mg or 110 mg within 1-4 hours of surgery followed by 150 mg or 220 mg daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and daily thereafter.
In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

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

detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.
Results of both studies showed that the antithrombotic effect of Pradaxa 220 mg and 150 mg were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of Major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 4). Better results were seen with the 220mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 4)."

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

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

In the studied patient population of RE-MODEL and RE-NOVATE (5539 patients treated), 51 % suffered from concomitant hypertension, 9 % from concomitant diabetes, 9 % from concomitant coronary artery disease and 20 % had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 4.

Data for the total VTE and all cause mortality endpoint are shown in table 5.

Data for adjudicated major bleeding endpoints are shown in tables 6 below.

Table 4: 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 ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	

Table 5: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	880	874	897
Incidences (%)	53 (6.0)	75 (8.6)	60 (6.7)
Risk ratio over	0.9	1.28	

enoxaparin			
95% CI	(0.63, 1.29)	(0.93, 1.78)	
RE-MODEL (knee)			
N	503	526	512
Incidences (%)	183 (36.4)	213 (40.5)	193 (37.7)
Risk ratio over enoxaparin	0.97	1.07	
95% CI	(0.82, 1.13)	(0.92, 1.25)	

Table 6: 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)

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 Cmax 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 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.

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.
Cmax 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.

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 4.2, 4.3 and 4.4).

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 4.2 and 4.4).

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 4.2 and 4.4).

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 section 4.2 and 4.4).

Gender:
Active substance exposure in female patients is about 40 % to 50 % higher than in male patients and no dose adjustment is recommended.

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.

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 repeat-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).

Carcinogenicity studies have not yet been completed with dabigatran.

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 2 years

Once the bottle is opened, the product must be used within 30 days

6.4 Special precautions for storage

Blister:

Store in the original package in order to protect from moisture

Bottle:

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, or 60 x 1 hard capsules) in coated aluminium perforated unit dose blisters. The aluminium unit dose blister is coated with polyvinylchloridevinylacetate copolymers acrylate (PVACAC) and polyvinylchlorid (PVC)).

Polypropylene bottle with a screw cap containing 60 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When taking Pradaxa capsules out of the blister pack, the following instructions should be followed:

- The hard capsules should be taken out of the blister card by peeling off the backing foil.
- The hard capsules should not be pushed through the blister foil.
- The blister foil should only be peeled off, when a hard capsule is required.

When taking a hard capsule out of the bottle, please observe the following instructions:

- The cap opens by pushing and turning.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 4.0 dated 30 July 2007 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 01 dated 11 January 2007 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR BLISTER for 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM YYYY

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 75 mg