PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Pradaxa® 75 mg
Pradaxa® 110 mg
Pradaxa® 150 mg

Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **PRADAXA 75 mg** capsule contains 75 mg of dabigatran etexilate base (as mesilate salt).
Each **PRADAXA 110 mg** capsule contains 110 mg of dabigatran etexilate base (as mesilate salt).
Each **PRADAXA 150 mg** capsule contains 150 mg of dabigatran etexilate base (as mesilate salt).
The capsules are sugar free.

3. PHARMACEUTICAL FORM

Capsules

PRADAXA 75 mg capsules: Oblong imprinted capsules (size 2) with a white, opaque cap and a white, opaque body filled with yellowish spherical pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R75.

PRADAXA 110 mg capsules: Oblong imprinted capsules (size 1) with a light blue, opaque cap and a light blue, opaque body filled with yellowish spherical pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R110.

PRADAXA 150 mg capsules: Oblong imprinted capsules (size 0) with a light blue, opaque cap and a white, opaque body filled with yellowish spherical pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R150.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

4.2 Posology and method of administration

PRADAXA can be taken with or without food. PRADAXA should be taken with a glass of water, to facilitate delivery to the stomach. If gastrointestinal symptoms develop it is

recommended to take PRADAXA with a meal and/or a proton pump inhibitor such as pantoprazole.
Do not open the capsule.

Instructions for use/handling:
When removing a capsule from the blister, please note the following instructions:
- Tear off one individual blister from the blister card along the perforated line
- Peel off the backing foil and remove the capsule
- The capsule should not be pushed through the blister foil

Adults
Prevention of venous thromboembolism (VTE) in patients following hip and knee replacement surgery: The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg.
Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of PRADAXA is 150 mg once daily.

VTE prevention following knee replacement surgery: Treatment with PRADAXA should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 10 days. 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.
Patients with moderate renal impairment have an increased risk for bleeding. For those patients the PRADAXA 75 mg capsules should be used instead of the 110 mg capsules.

VTE prevention following hip replacement surgery: Treatment with PRADAXA should be initiated orally within 1 - 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28 days. 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.
Patients with moderate renal impairment have an increased risk for bleeding. For those patients the PRADAXA 75 mg capsules should be used instead of the 110 mg capsules.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg capsules twice daily. Therapy should be continued life-long.

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE): The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg capsules twice daily following treatment with a parenteral anticoagulant for at least 5 days. Therapy should be continued for up to 6 months.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg capsules twice daily. Therapy could be continued life-long depending on the individual patient's risk factors.

Children
PRADAXA has not been investigated in patients < 18 years of age. Treatment of children with PRADAXA is not recommended.

Renal impairment
Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 mL/min).
There are no data to support use in patients with severe renal impairment (CrCl < 30 mL/min); treatment in this population with PRADAXA is not recommended (see section 4.3).

While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolaemia, dehydration, and with certain co-medications that may decrease renal function such as with initiation of chemotherapeutics, or amphotericin B or under chronic treatment with NSAIDs).

PRADAXA can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery: Dosing should be reduced to 150 mg PRADAXA taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment (CrCl 30 - 50 mL/min).

Treatment with PRADAXA should be initiated orally within 1 - 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28 days (following hip replacement surgery). 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.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:
In patients with moderate renal impairment (CrCl 30 - 50 mL/min) the renal function should be assessed at least once a year.
No dose adjustment is necessary. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE): No dose adjustment is necessary in patients with renal function over CrCl 30 mL/min. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): In patients with moderate renal impairment (CrCl 30 - 50 mL/min) the renal function should be assessed at least once a year.
No dose adjustment is necessary in patients with renal function over CrCl 30 mL/min. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Elderly
Pharmacokinetic studies in older subjects demonstrate an increase in dabigatran exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 mL/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolaemia, dehydration, and with certain co-medications that may decrease renal function such as with initiation of chemotherapeutics, or amphotericin B or under chronic treatment with NSAIDs). (See also section 4.2; *Renal impairment*.)

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery: No dose adjustment is necessary, patients should be treated with 220 mg PRADAXA taken once daily as 2 capsules of 110 mg.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: Patients aged 80 years or above should be treated with a daily dose of 220 mg taken orally as 110 mg capsules twice daily.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): No dose adjustment is necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Weight
No dose adjustment is necessary.

Concomitant use of PRADAXA with strong P-glycoprotein inhibitors, i.e. amiodarone, quinidine or verapamil
Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery: Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive PRADAXA and amiodarone, quinidine or verapamil (see section 4.5).

Treatment initiation with verapamil should be avoided in patients who have undergone hip and knee replacement surgery who are already treated with PRADAXA. Simultaneous initiation of treatment with PRADAXA and verapamil should also be avoided.

Treatment with PRADAXA should be initiated orally within 1 - 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28 days (following hip replacement surgery). 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.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: No dose adjustment is necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): No dose adjustment is necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Patients at risk of bleeding

The presence of the following factors is associated with an increased risk of bleeding: e.g. age ≥ 75 years, moderate renal impairment (CrCl 30 - 50 mL/min), concomitant treatment with strong P-gp inhibitors (see section 4.5), antiplatelet medicines or previous gastro-intestinal bleed (see sections 4.3 and 4.4).

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: For patients with one or more than one of these risk factors, a reduced daily dose of 220 mg given as 110 mg twice daily may be considered at the discretion of the doctor.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): No dose adjustment is necessary for patients with single risk factors. Only limited clinical data are available for patients with multiple risk factors. Therefore, PRADAXA should only be given in these patients if the expected benefit outweighs bleeding risks.

Switching from PRADAXA treatment to a parenteral anticoagulant

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery: Wait 24 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: Wait 12 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): Wait 12 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

Switching from parenteral anticoagulant treatment to PRADAXA

PRADAXA should be given within 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 UFH).

Switching from warfarin to PRADAXA

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: The warfarin should be stopped. PRADAXA can be given as soon as the INR is < 2,0.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): The warfarin should be stopped. PRADAXA can be given as soon as the INR is < 2,0.

Switching from PRADAXA to warfarin

The starting time of warfarin should be adjusted according to the patient's CrCl as follows:

- CrCl ≥ 50 mL/min, start warfarin 3 days before discontinuing PRADAXA
- CrCl ≥ 30 - < 50 mL/min, start warfarin 2 days before discontinuing PRADAXA.

Cardioversion
To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:
Patients can stay on PRADAXA while being cardioverted.

Catheter ablation for atrial fibrillation
Catheter ablation can be conducted in non-valvular atrial fibrillation patients on 150 mg twice daily PRADAXA treatment. PRADAXA treatment does not need to be interrupted. There are no clinical data on continuation of PRADAXA treatment during catheter ablation in those non-valvular atrial fibrillation patients receiving 110 mg twice daily.

Percutaneous coronary intervention (PCI) with stenting
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.

Missed dose
Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery: patients should continue with their remaining daily doses of PRADAXA at the same time on the next day and not take a double dose to make up for missed individual doses.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: 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, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): 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, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses.

Discontinuation rules before invasive or surgical procedures

Renal function (CrCl in mL/min)	Estimated half-life (hours)	Stop PRADAXA 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)

*for more details see the table in section 5.2 and section 4.4.

4.3 Contraindications
- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of PRADAXA
- Patients with severe renal impairment (CrCl < 30 mL/min)

- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis
- Moderate to severe hepatic impairment (Child-Pugh B/C)
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months
- Patients with an indwelling spinal or epidural catheter and during the first hour after removal (see section 4.4)
- Prolonged co-administration with heparins or warfarin
- Concomitant treatment with systemic ketoconazole (see section 4.5)
- The following treatments should not be administered concomitantly with PRADAXA: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, ticagrelor, 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 and that PRADAXA and Vitamin K antagonists (e.g. warfarin) can be administered together, but only for a few days during switching from PRADAXA to Vitamin K antagonist treatment
- In patients with suspected infective endocarditis
- Prosthetic heart valve replacement

4.4 Special warnings and precautions for use

Haemorrhagic risk

PRADAXA increases the risk of bleeding and can cause significant and sometimes fatal bleeding. PRADAXA should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with PRADAXA. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should prompt a search for a bleeding site. In the case of haemorrhagic complications treatment must be discontinued and the source of bleeding investigated. For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent idarucizumab is available (See *Surgery and interventions*, *Pre-operative phase* and section 4.9).

Careful clinical monitoring including renal function testing is required in certain clinical situations (see sections 5.1 and 4.2).

PRADAXA does not in general require routine anticoagulation monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Coagulation testing should also be considered to assist with the management of patients in the perioperative setting, suspected overdose and emergency situations.

The INR test is unreliable in patients on PRADAXA and false positive INR elevations have been reported. Therefore INR tests should not be performed. Tests of anticoagulant activity such as Thrombin Time (TT), diluted Thrombin Time (dTT), Ecarin Clotting Time (ECT) and activated Partial Thromboplastin Time (aPTT) are available to detect excessive dabigatran activity.

PRADAXA related anticoagulation can be assessed by ECT or TT. If ECT or TT are not available, the aPTT test provides an approximation of PRADAXA's anticoagulant activity.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:
In atrial fibrillation patients treated with 150 mg twice daily an aPTT of greater than 2,0 – 3,0 fold of normal range at trough was associated with an increased risk of bleeding.

Renal impairment
Renal function should be assessed by calculating the creatinine clearance (CrCl) by the Cockgroft-Gault method prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 mL/min).
Patients who develop acute renal failure should discontinue PRADAXA.

Patients with antiphospholipid syndrome
Patients with antiphospholipid syndrome (especially if triple-positive for antiphospholipid antibodies) are at an increased risk for thromboembolic events.
While the efficacy of PRADAXA is established for the treatment and prevention of venous thromboembolism it has not been studied specifically in the subpopulation of patients with antiphospholipid syndrome.
Therefore, careful consideration of all treatment options (including standard treatment such as vitamin K antagonists) is recommended before use of PRADAXA in patients with antiphospholipid syndrome.

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 (see also section 5.2).

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).

In case of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effect is required the specific reversal agent idarucizumab to PRADAXA is available.

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

Pre-operative phase
Due to an increased risk of bleeding PRADAXA should be stopped temporarily in advance of invasive or surgical procedures.

Emergency surgery or urgent procedure
The specific reversal agent idarucizumab of PRADAXA is available for the rapid reversal of the anticoagulation effect (see *Surgery and interventions*).

Acute surgery/intervention
PRADAXA should be temporarily discontinued. An acute surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed

there may be an increase in the risk of bleeding. Neuraxial blocks are not recommended for within 24 hours after discontinuation of PRADAXA. Refer to *Haemorrhagic risk* above for information regarding correlation between plasma dabigatran concentration and degree of anticoagulant effect.

Elective surgery/intervention/spinal anaesthesia/epidural anaesthesia/lumbar puncture
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. Clearance of PRADAXA in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see section 5.2 and the table summarising discontinuation rules under section 4.2).

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 1 hour 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.

PRADAXA is contraindicated in patients with severe renal dysfunction (CrCl < 30 mL/min) but, should this occur, then PRADAXA should be stopped at least 5 days before major surgery.

If an acute intervention is required, 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 there may be an increase in the risk of bleeding. This risk of bleeding should be weighed together with the urgency of intervention.

Post-procedural period
PRADAXA treatment can be resumed/started after complete haemostasis is achieved.

Amiodarone
PRADAXA exposure in healthy subjects was increased by 60 % in the presence of amiodarone.

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of a central venous or arterial catheter or during catheter ablation for atrial fibrillation) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, Vitamin K antagonists, and the P-gp inhibitors such as but not limited to itraconazole, tacrolimus, ciclosporin, ritonavir, tipranavir, nelfinavir and saquinavir.

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

The concomitant use of dronedarone increases exposure of PRADAXA and is not recommended. See section 4.5.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs).

Use of fibrinolytic agents for the treatment of acute ischaemic stroke
The use of fibrinolytic agents for the treatment of acute ischaemic stroke may be considered if the patient presents with a thrombin time (TT), or ecarin clotting time (ECT), or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range.
In situations where there is an increased haemorrhagic risk (e.g. recent biopsy or major trauma, bacterial endocarditis) close observation (looking for signs of bleeding or anaemia) is generally required.
If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in haemoglobin is suggested.

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery
NSAIDs given for short-term peri-operative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with PRADAXA.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation
Co-administration of anti-platelet (including aspirin, clopidogrel and ticagrelor) and NSAID therapies increase the risk of bleeding. Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥ 75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in haemoglobin is suggested.

Interaction with P-gp inducers
The concomitant use of PRADAXA with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's wort (Hypericum perforatum) or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction
The concomitant use of PRADAXA with treatments that act on haemostasis or coagulation including Vitamin K antagonists and anti-platelet medicines can markedly increase the risk of bleeding. (See sections 4.3 and 4.4.)

PRADAXA is not metabolised by the cytochrome P450 system and *in vitro* interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. Therefore related interactions are not expected with PRADAXA. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following medicines: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Atorvastatin
When PRADAXA was co-administered with atorvastatin, a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of PRADAXA were unchanged indicating a lack of interaction.

Diclofenac
When PRADAXA was co-administered with diclofenac, a CYP2C9 substrate, pharmacokinetic properties of both medicines remained unchanged indicating a lack of interaction between PRADAXA and diclofenac.

P-gp inhibitor/inducer interactions
The pro-drug dabigatran etexilate, but not dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp). Therefore co-medications with P-gp transporter inhibitors and inducers have been investigated.

P-glycoprotein inhibitors
Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor, clarithromycin and the fixed-dose combination glecaprevir/pibrentasvir) is expected to result in increased PRADAXA plasma concentrations. (See section 4.2.)

Concomitant administration of systemic ketoconazole is contraindicated.

Amiodarone
PRADAXA exposure in healthy subjects was increased by 1,6 fold (+ 60 %) in the presence of amiodarone.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation
PRADAXA concentrations were increased by no more than 14 % and no increased risk of bleeding was observed.

Dronedarone
When PRADAXA and dronedarone were given at the same time total PRADAXA $AUC_{0-\infty}$ and C_{max} values increased by about 2,4 fold and 2,3 fold (+ 136 % and 125 %), respectively, after multiple dosing of 400 mg dronedarone twice daily, and about 2,1 fold and 1,9 fold (+ 114 % and 87 %), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of PRADAXA were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 hours after PRADAXA, the decreases in dabigatran $AUC_{0-\infty}$ were 1,3 fold and 1,6 fold, respectively. (See section 4.4.)

Verapamil
When PRADAXA (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.

The greatest elevation of PRADAXA exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to PRADAXA intake (increase of C_{max} by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increase

of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increase of C_{max} by about 60 % and AUC by about 50 %). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after PRADAXA (increase of C_{max} by about 10 % and AUC by about 20 %). This is explained by completed dabigatran absorption after 2 hours. (See section 4.2.)

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

Quinidine
Quinidine was given as a 200 mg dose every 2nd hour up to a total dose of 1 000 mg. PRADAXA was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. PRADAXA $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 1,5 fold (+53 % and 56 %), respectively, with concomitant quinidine.

Clarithromycin
When clarithromycin 500 mg twice daily was administered together with PRADAXA no clinically relevant pharmacokinetic (PK)-interaction was observed (increase of C_{max} by about 15 % and AUC by about 19 %).

Ketoconazole
Systemic ketoconazole increased total PRADAXA $AUC_{0-\infty}$ and C_{max} values by about 2,4 fold (+138 % and 135 %, respectively), after a single dose of 400 mg, and 2,5 fold (+153 % and 149 %, respectively), after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (see section 4.3).

Ticagrelor
When a single dose of 75 mg PRADAXA was co-administered 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 (+ 73 % and 95 %), respectively. After multiple doses of ticagrelor 90 mg twice daily the increase of dabigatran exposure after a single dose is reduced to 1,56 fold and 1,46 fold (+ 56 % and 46 %) for C_{max} and AUC, respectively.
Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg PRADAXA (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and by $C_{max,ss}$ by 1,49 fold and 1,65 fold (+ 49 % and 65 %), respectively, compared with PRADAXA given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg PRADAXA (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1,27 fold and 1,23 fold (+ 27 % and 23 %), respectively, compared with PRADAXA given alone. Concomitant administration of 90 mg ticagrelor twice daily (maintenance dose) with 110 mg PRADAXA increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1,26 fold and 1,29 fold, respectively, compared with PRADAXA given alone.

P-glycoprotein substrate
Digoxin:
When PRADAXA was co-administered with digoxin, a P-gp substrate, no changes in digoxin and no clinically relevant changes in PRADAXA exposure have been observed.

Neither dabigatran nor the pro-drug dabigatran etexilate is a clinically relevant P-gp inhibitor.

P-glycoprotein inducers
Rifampicin
Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total PRADAXA peak and total exposure by 65,5 % and 67 %, respectively. The inducing effect was diminished resulting in PRADAXA exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.
The concomitant use with P-gp inducers (e.g. rifampicin) reduces exposure to PRADAXA and should be avoided (see section 4.4).

Platelet-inhibitors
Acetylsalicylic acid (ASA)
The effect of concomitant administration of PRADAXA and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomised ASA co-administration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg PRADAXA twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively.

From the data gathered in the phase III study, it was observed that ASA or clopidogrel co-medication with PRADAXA at dosages of 110 or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation
NSAIDs increased the risk of bleeding.

Clopidogrel
In a phase I study in young healthy male volunteers, the concomitant administration of PRADAXA and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. However, with a loading dose of 300 or 600 mg clopidogrel, PRADAXA $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 1,3 to 1,4 fold (+ 30 to 40 %). (See above subsection on ASA.) (See section 4.3.)

Selective serotonin re-uptake inhibitors (SSRIs)
SSRIs increased the risk of bleeding (see section 4.4).

Gastric pH-elevating agents
The changes in PRADAXA exposure determined by population pharmacokinetic analysis caused by proton pump inhibitors and antacids were not considered clinically relevant because the magnitude of the effects were minor (fractional decrease in bioavailability not significant for antacids and 14,6 % for PPIs).

4.6 Fertility, pregnancy and lactation
Safety in pregnancy and lactation has not been established.

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

4.8 Undesirable effects
Bleeding
Bleeding is the most relevant side effect of PRADAXA. Depending on the indication, bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, in long-term treatment in nearly 16,6 % of patients with atrial fibrillation treated for the reduction of risk of stroke and systemic embolism and in 14,4 % of patients with acute DVT and/or PE. In the recurrent DVT/PE trials 19,4 % and 10,5 % of patients experienced any bleeding in the active controlled and placebo controlled studies, respectively.

Major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Known bleeding complications from any organ including anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Side effects in general
Adverse reactions classified by System Organ Class and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below. A second list with indication-specific side effects is also provided.
Frequency classes: 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); Not known (cannot be estimated from the available information).

Side effects identified independent from indication, i.e. including:
- *Risk reduction of thromboembolic stroke and systemic embolism in patients with atrial fibrillation (SPAF) with PRADAXA dosages of 110 or 150 mg taken twice daily.*
- *Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (aVTEt) with a PRADAXA dosage of 150 mg taken twice daily.*
- *Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (sVTEp) with a PRADAXA dosage of 150 mg taken twice daily.*
- *Primary VTE prevention (pVTEp) studies after hip and knee replacement surgery with PRADAXA dosages of 220 or 150 mg taken once daily.*

MedDRA preferred term	*Frequency in SPAF*	*Frequency in pVTEp*	*Frequency in aVTEt*	*Frequency in sVTEp*
Patients	***12 042***	***6 684***	***2 553***	***2 114***
Blood and the lymphatic system disorders				
Anaemia	Common	Uncommon	Uncommon	Rare
Thrombocytopenia	Uncommon	Rare	Rare	Rare
Immune system disorders				
Hypersensitivity	Uncommon	Uncommon	Uncommon	Uncommon

MedDRA preferred term	*Frequency in SPAF*	*Frequency in pVTEp*	*Frequency in aVTEt*	*Frequency in sVTEp*
Patients	*12 042*	*6 684*	*2 553*	*2 114*
Pruritis	Uncommon	Rare	Rare	Uncommon
Rash	Uncommon	Rare	Uncommon	Uncommon
Urticaria	Rare	Rare	Rare	Rare
Bronchospasm	Not known	Not known	Not known	Not known
Anaphylactic reaction	Not known	Not known	Not known	Not known
Angioedema	Rare	Rare	Rare	Rare
Nervous system disorders				
Intracranial haemorrhage	Uncommon	Rare	Rare	Rare
Vascular disorders				
Haematoma	Uncommon	Uncommon	Uncommon	Uncommon
Haemorrhage	Uncommon	Rare	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders				
Epistaxis	Common	Uncommon	Common	Common
Haemoptysis	Uncommon	Rare	Uncommon	Uncommon
Gastrointestinal disorders				
Gastrointestinal haemorrhage	Common	Uncommon	Common	Common
Abdominal pain	Common	Rare	Uncommon	Uncommon
Diarrhoea	Common	Uncommon	Uncommon	Uncommon
Dyspepsia	Common	Rare	Common	Common
Dysphagia	Uncommon	Rare	Rare	Rare
Gastrointestinal ulcer, including oesophageal ulcer	Uncommon	Rare	Uncommon	Rare
Gastro-oesophagitis	Uncommon	Rare	Uncommon	Uncommon
Gastro-oesophageal reflux disease	Uncommon	Rare	Uncommon	Uncommon
Nausea	Common	Uncommon	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon	Uncommon	Uncommon
Hepatobiliary disorders				
Abnormal hepatic function	Uncommon	Common	Uncommon	Uncommon
Skin and subcutaneous tissue disorders				
Skin haemorrhage	Common	Uncommon	Common	Common
Musculoskeletal, connective tissue and bone disorders				
Haemarthrosis	Rare	Uncommon	Uncommon	Rare
Renal and urinary disorders				
Urogenital haemorrhage	Common	Uncommon	Common	Common
Haematuria	Common	Uncommon	Common	Common
General disorders and administration site conditions				
Injection site haemorrhage	Rare	Rare	Rare	Rare
Catheter site haemorrhage	Rare	Rare	Rare	Rare
Injury, poisoning and procedural complications				
Traumatic haemorrhage	Rare	Uncommon	Uncommon	Rare
Incision site haemorrhage	Rare	Rare	Rare	Rare

Other side effects identified specifically from the studies in the indication primary VTE prevention after hip and knee replacement surgery
Vascular disorders
Uncommon: wound haemorrhage

General disorders and administration site conditions
Rare: bloody discharge

Injury, poisoning and procedural complications
Uncommon: post procedural haematoma, post procedural haemorrhage, post procedural discharge, wound secretion
Rare: post operative anaemia

Surgical and medical procedures
Rare: wound drainage, post procedural drainage

Post-marketing experience
The following side effects have been identified during post-approval use of PRADAXA therefore the frequency is not known:

Blood and the lymphatic system disorders
Neutropenia, agranulocytosis

Skin and subcutaneous tissue disorders
Alopecia

Renal and urinary disorders
Anticoagulant-related nephropathy

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 Overdose
Symptoms
Overdose following administration of PRADAXA may lead to haemorrhagic complications due to its pharmacodynamic properties.

Therapy
A specific reversal agent antagonising the pharmacodynamic effect of PRADAXA is available, namely idarucizumab. (See section 4.4 - *Haemorrhagic risk*; *Surgery and interventions*, *Pre-operative phase*.) In the event of haemorrhagic complications, treatment

must be discontinued and the source of bleeding investigated. Since PRADAXA is excreted predominantly by the renal route adequate diuresis must be maintained.
Depending on the clinical situation appropriate standard treatment, e.g. surgical haemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma.

Coagulation factor concentration (activated or non-activated) or recombinant Factor VIIa may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of PRADAXA, but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicines have been used. All symptomatic treatment has to be given according to the doctor's judgement.

As protein binding is low, PRADAXA is dialysable, however there is limited clinical experience in using dialysis in this setting (see section 5.2, *Special populations, Renal insufficiency*).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 8.2 Anticoagulants.

Dabigatran etexilate is a small molecule pro-drug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and then converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a 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 correlation between plasma dabigatran concentration and degree of anticoagulant effect. Prothrombin time (PT, expressed as International Normalised Ratio (INR)) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity. Ecarin Clotting Time (ECT), Thrombin Time (TT) and diluted Thrombin Time (dTT) are sensitive assays that increase in direct proportion to dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher dabigatran concentrations (see section 4.4, *Haemorrhagic risk*). ECT, TT and aPTT are not standardised or validated with dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the presence or absence of the anticoagulant effect of dabigatran.

Interpretation of coagulation assay results should consider time of PRADAXA administration relative to time of blood sampling (see section 5.2).
In patients undergoing elective hip replacement surgery, greater test variability with aPTT and ECT was observed. The mechanisms for this variability immediately after surgery are unclear and aPTT and ECT levels measured in the first 2-3 days following surgery should be interpreted with caution.
Whilst PRADAXA does not require routine laboratory anticoagulant monitoring, careful clinical monitoring including renal function testing is required in certain clinical situations (see section 4.4, *Haemorrhagic risk* and section 4.2).

5.2 Pharmacokinetic properties

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with peak concentration (C_{max}) attained within 0,5 and 2,0 hours post administration. C_{max} and the area under the plasma concentration-time curve (AUC) were dose proportional. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of approximately 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. However, half-life is prolonged if renal function is impaired as shown in the table below.

Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

glomerular filtration rate (CrCl)	gMean (gCV%; range) half-life
[mL/min]	[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)

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6,5 %.

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentration by 2 hours.

The oral bioavailability may be increased by 1,4 fold (+ 37 %) compared to the reference capsule formulation when the pellets are taken without the capsule shell. Hence, the integrity of the capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and take the pellets alone (e.g. sprinkled over food or into beverages). (See Section 4.2.)

Post-operative absorption of dabigatran etexilate, 1 - 3 hours following surgery is relatively slow compared with that in healthy volunteers. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery. It is noted, however, that contributing factors such as anaesthesia, gastrointestinal paresis and surgical effects will mean that a proportion of patients will exhibit absorption delay independent of the oral medicine formulation. Slow and delayed absorption is usually only present on the day of

surgery. On subsequent post-surgery days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicine administration.

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.

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the pro-drug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. 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.

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.

Special populations
Renal insufficiency
The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate 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 and 4.3).

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

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation
Almost half (45,8 %) of the patients studied had a CrCl > 50 - < 80 mL/min. Patients with moderate renal impairment (CrCl between 30 - 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 $\geq$ 80 mL/min).

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE)
21,7 % of patients had mild renal impairment (CrCl > 50 - < 80 mL/min) and 4,5 % of patients had moderate renal impairment (CrCl between 30 - 50 mL/min). Patients with mild and moderate renal impairment had on average 1,7 fold and 3,4 fold higher steady state dabigatran trough concentrations, respectively, compared with patients with CrCl > 80 mL/min.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE)
22,9 % and 22,5 % of the patients studied had a CrCl > 50 - < 80 mL/min, and 4,1 % and 4,8 % had a CrCl between 30 - 50 mL/min.

Hepatic insufficiency
No change in dabigatran exposure was seen in 12 volunteers with moderate hepatic insufficiency (Child-Pugh B) compared to 12 controls in a phase 1 study. In clinical trials, patients with Child-Pugh classification B and C, or liver disease expected to have any impact on survival, including hepatitis A, B or C, or with elevated enzymes $\geq$ 2 Upper Limit of Normal (ULN) were excluded.

Elderly patients
Specific pharmacokinetic studies with elderly subjects showed an increase of 1,4 to 1,6 fold (+ 40 to 60 %) in the AUC and of more than 1,25 fold (+ 25 %) in C_{max} compared to young subjects.
The $AUC_{\tau,ss}$ and $C_{max,ss}$ in male and female elderly subjects (> 65 years) were approximately 1,9 fold and 1,6 fold higher for elderly females compared to young females and 2,2 and 2,0 fold higher for elderly males than in male subjects of 18 - 40 years of age.
The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

The effect by age on exposure to dabigatran was confirmed in the reduction of risk of stroke in atrial fibrillation study with an about 1,3 fold (+ 31 %) higher trough concentration for subjects $\geq$ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

Body weight
The dabigatran trough concentrations were about 20 % lower in patients with a BW > 100 kg compared with 50 – 100 kg. The majority (80,8 %) of the subjects were in the $\geq$ 50 kg and < 100 kg category with no clear difference detected. Limited data in patients $\leq$ 50 kg are available.

Gender
Dabigatran exposure in the primary VTE prevention studies was about 1,4 to 1,5 fold (+ 40 % to 50 %) higher in female patients.

In atrial fibrillation patients, females had on average 1,3 fold (+ 30 %) higher trough and post-dose concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: acacia, dimeticone 350, hydroxypropyl cellulose, hypromellose, talc, tartaric acid.
Capsule shell: carrageenan, hypromellose, Indigo Carmin (E132) (PRADAXA 110 and 150 mg only), potassium chloride, titanium dioxide.
Printing ink: ammonia solution, ethanol anhydrous, iron oxide black (E172), isopropyl alcohol, butyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C in the original package in order to protect from moisture. Keep the blisters in the carton until required for use.
Do not put the capsules in pill boxes or pill organizers, unless capsules can be maintained in the original blister.
Keep out of reach of children.

6.5 Nature and contents of container

PRADAXA 75 and 110 mg capsules: cartons containing 30 or 60 capsules, packed in aluminium blister strips of 10 capsules per strip.
PRADAXA 150 mg capsules: cartons containing 60 capsules, packed in aluminium blister strips of 10 capsules per strip.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
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Tel. No.: + 27-(0)11-348 2400

8. REGISTRATION NUMBERS

PRADAXA 75 mg capsules: 42/8.2/0130
PRADAXA 110 mg capsules: 42/8.2/0131
PRADAXA 150 mg capsules: 45/8.2/0162

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Dates of registration: 19 March 2010 (75 mg & 110 mg); 14 September 2012 (150 mg)

10. DATE OF REVISION OF THE TEXT

28 February 2025

BOTSWANA Reg. No.		
PRADAXA 75 mg	BOT1001712	S2
PRADAXA 110 mg	BOT1001713	
PRADAXA 150 mg	BOT1202053	

NAMIBIA Reg. No.		
PRADAXA 75 mg	10/8.2/0494	NS2
PRADAXA 110 mg	10/8.2/0495	
PRADAXA 150 mg	11/8.2/0013	