Any adverse reactions should be reported in accordance with the Saudi Vigilance spontaneous reporting system to:
The National Pharmacovigilance and Drug Safety Centre NPC
Email: npc.drug@sfda.gov.sa
Fax: +966112057662
Phone +966-11-2038222 Ext : 2317 -2356- 2353-2354- 2334-2340
Toll free phone: 8002490000

In addition, suspected adverse reactions related Boehringer Ingelheim products may be reported to Boehringer Ingelheim Pharmacovigilance department:
Email: PV_local_Saudi_Arabia@boehringer-ingelheim.com
Phone: +966-11-207 8275

References:
1. PRADAXA Summary of Product Characteristics 2013. Boehringer Ingelheim. 2. Connolly SJ et al. N Engl J Med 2009;361(12):1139–1151 3. Connolly SJ et al. N Engl J Med 2010;363(19):1875–1876 (appendix). 4. Wann LS et al. Circulation 2011;123:1144–1150. 5. CammtAJ e al. Eur Heart J 2012;33:2719–2747. 6. Ogawa S et al. Circ J 2011;75:2719–2721. 7. National Institute for Health and Care Excellence (2012 TA249. London: National Institute for Health and Care Excellence. 8. Boehringer Ingelheim. Data on file. 9. Ezekowitz MD et al. Am Heart 2009; 157:805–810. 10. Southworth M et al. N Engl J Med 2013;368(14):1272–1274. 11. EMA. Questions and answers on the review o bleeding risk with Pradaxa (dabigatran etexilate). Made available 24 May 2012. 12. van Ryn J et al. Thromb Haemost 2010; 103:1116–1127 13. Liesenfeld K-H et al. Br J Clin Pharmacol 2006; 62:527–537. 14. Stangier J et al. Br J Clin Pharmacol 2007; 64:292–303. 15. Hemöclot thrombin inhibitor assay (Hyphen BioMed, Neuville-sur Oise, France). www.clottingtesting.com 16. HemosIL® assay (Instrumentatio Laboratory, Werfen Group, Barcelona, Spain). www.instrumentationlaboratory.com 17. Technoclot® DTI Dabigatran assay (Technoclon GmbH, Vienna, Austria). www.technoclone.com/products/coagulation/control-plasma/dabigatran-cont. 18.Vang ML et al. Act Anaesthesiol 2011; 55(5):507-516. 19. Warfarin Summary of Product Characteristics, 2010. Rosemont Pharmaceuticals Limited. 20 Ezekowitz MD et al. Am Heart J 2009; 157:805-810.

Boehringer Ingelheim
Boehringer Ingelheim Middle East, Turkey, and Africa Regional Operating Unit
P.O. Box 505123, Dubai Healthcare City, Dubai, United Arab Emirates
Website: www.boehringer-ingelheim.com/mena/
Tel: +971 4 4230400 Fax: +971 4 4233637

This guide provides recommendations for the use of Pradaxa.

Pradaxa® (dabigatran etexilate) PRESCRIBER GUIDE

The recommendations only refer to the indications:

- Stroke prevention in atrial fibrillation
- Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Prevention of recurrent DVT and PE in adults (DVT/PE)

Important Safety information

This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks and therefore it is advised to be read carefully before prescribing/dispensing/administering the product

Pradaxa dabigatran etexilate Experienced Protection

Indication

PRADAXA is indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more of the following risk factors:[1]

- Previous stroke, transient ischemic attack, or systemic embolism (SEE)
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

Treatment of DVT and PE, and prevention of recurrent DVT/PE in adults

Please see full Summary of Product Characteristics included with this guide.

PRADAXA is contraindicated in patients with:[1]

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with severe renal impairment (CrCL < 30 mL/min)
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone.
- Prosthetic heart valves requiring anticoagulant treatment

Please see full Summary of Product Characteristics included with this guide.

DVT/PE dose:

Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (DVT/PE):

The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

RECOMMENDED DAILY DOSE

PRADAXA 150 mg TWICE DAILY

Please see full Summary of Product Characteristics included with this guide.

SPAF dose:

RECOMMENDED DAILY DOSE

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:

The recommended daily dose of Pradaxa is 300 mg taken orally as one 150 mg capsule twice daily. Therapy should be continued long term.

LOWER DOSE FOR SPECIAL POPULATIONS*

LOWER DOSE FOR SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Reduced daily dose of 220 mg (taken as one 110 mg capsule twice daily) recommended:

- **Patients aged 80 years or above** should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily
- In patients who receive **concomitantly Pradaxa and verapamil**, dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily

Reduced daily dose of 220 mg (taken as one 110 mg capsule twice daily) for consideration:

- Patients between 75-80 years
- Patients with moderate renal impairment (CrCl 30-50 ml/min)
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

Please see full Summary of Product Characteristics included with this guide.

Method of administration

- Pradaxa can be taken with or without food. The capsule should be swallowed whole with a glass of water, to facilitate delivery to the stomach
- Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding

RECOMMENDATION FOR KIDNEY FUNCTION MEASUREMENT IN ALL PATIENTS

Renal function should be assessed by calculating the CrCL by the Cockcroft-Gault* method prior to initiation of treatment with Pradaxa in order to exclude patients with severe renal impairment (i.e. CrCL <30 mL/min) from treatment.

- While on treatment, renal function should be assessed at least once a year or more frequently in certain clinical situations when it is suspected that renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications)
- In elderly patients (>75 years) or patients with renal impairment, the renal function should be assessed at least once a year

***Cockcroft-Gault formula**

For creatinine in mg/dL

$$\frac{(140\text{-age } [\textit{years}]) \times \text{weight } [\textit{kg}] \ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine } [\textit{mg/dL}]}$$

For creatinine in µmol/L

$$\frac{1.23 \times (140\text{-age } [\textit{years}]) \times \text{weight } [\textit{kg}] \ (\times 0.85 \text{ if female})}{\text{serum creatinine } [\textit{µmol/L}]}$$

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment.

Please see full Summary of Product Characteristics included with this guide.

SPECIAL PATIENT POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Patients with an increased bleeding risk (see Table 1 overleaf) should be closely monitored clinically (looking for signs of bleeding or anemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test (see "Coagulation tests and their interpretation") may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose of 220 mg given as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted. As with all anticoagulants, Pradaxa should be used with caution in conditions with an increased risk of bleeding. Bleeding may occur at any site during therapy with Pradaxa. An unexplained fall in hemoglobin and/ or hematocrit or blood pressure should lead to a search for a bleeding site. Close clinical surveillance is recommended throughout the treatment period, especially if risk factors are combined.

Table 1* summarizes factors which may increase the hemorrhagic risk

Pharmacodynamic and kinetic factors	Age ≥75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30–50 mL/min CrCL)† • P-gp† inhibitor comedication (some P-gp inhibitors are contraindicated) Minor: • Low body weight (<50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs‡ • Other drugs which may impair hemostasis
Diseases/procedures with special hemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis, gastroesophageal reflux

* For special patient populations requiring a reduced dose, see the "Dosing" section.
† CrCL: Creatinine clearance; P-gp: P-glycoprotein; SSRIs: selective serotonin re-uptake inhibitors; SNRIs: serotonin norepinephrine re-uptake inhibitors.

Please see full Summary of Product Characteristics included with this guide.

Switching

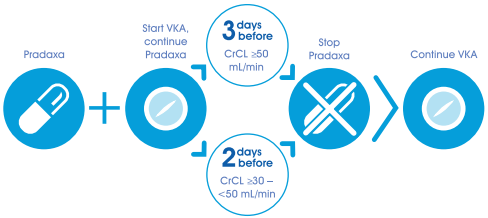
VKA to Pradaxa

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

Pradaxa treatment to Vitamin K antagonists (VKA)

Adjust the starting time of the VKA based on CrCL as follows:

- CrCL ≥50 mL/min, start VKA 3 days before discontinuing Pradaxa
- CrCL ≥30 – <50 mL/min, start VKA 2 days before discontinuing Pradaxa



NOAC to Pradaxa

Pradaxa can be initiated when the next dose of anticoagulant is due

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

Please see full Summary of Product Characteristics included with this guide.

Switching

Parenteral anticoagulants to Pradaxa

Discontinue the parenteral anticoagulant and start Pradaxa 0–2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous unfractionated heparin (UFH)

Previous injectable anticoagulant

Start Pradaxa 0–2 hours before next dose of injectable anticoagulant is due

Do not give due dose of injectable anticoagulant

Pradaxa treatment to parenteral anticoagulant

It is recommended to wait 12 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant.

Last dose of Pradaxa

Wait 12 hrs

Start injectable anticoagulant and stop Pradaxa

The 6 - hour rule for missing a dose

Time since missed dose	Recommendation
< 6 hours	The patient should take the "missed" dose
> 6 hours	The patient should wait until their next scheduled dose

Please see full Summary of Product Characteristics included with this guide.

CARDIOVERSION

Patients with non-valvular atrial fibrillation treated for prevention of stroke and systemic embolism can stay on Pradaxa while being cardioverted.

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.

Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

Please see full Summary of Product Characteristics included with this guide.

Preoperative phase

Table 2 summarizes discontinuation rules before invasive or surgical procedures

Renal function (CrCL mL/min)	Estimated half-life (hours)	Stop dabigatran 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)

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 against the urgency of intervention.

Please see full Summary of Product Characteristics included with this guide.

Coagulation tests and their interpretation

Pradaxa treatment does not need routine clinical monitoring, neither for short-term nor for long-term treatment.[13,14] However, in cases of suspected overdose or in patients treated with Pradaxa presenting in emergency departments, it may be advisable to assess the anticoagulation status. There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect.[1,12] **Thrombin time (TT)**, **ecarin clotting time (ECT)** and **activated partial thromboplastin time (aPTT)** may provide useful information, but the tests are not standardized, and results should be interpreted with caution.

aPTT

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

INR

The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed.

Measurement of dabigatran plasma concentrations

For a quantitative measurement of dabigatran plasma concentrations, several dabigatran assays based on diluted thrombin time (dTT) are available.[15-17] A dTT measure[1] of >200 ng/mL dabigatran plasma concentration prior to the next drug intake may be associated with a higher risk of bleeding.[1] A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran

Please see full Summary of Product Characteristics included with this guide.

Table 3 shows coagulation test thresholds at trough (i.e. prior to the next drug intake) that may be associated with an increased risk of bleeding. Please note: in the first 2–3 days after surgery, false prolonged measures may be detected[12,13]

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

Time point: Anticoagulant parameters depend on the time when the blood sample was taken relative to the time when the previous dose was given. A blood sample taken 2 hours after Pradaxa ingestion (~peak level) will have different (higher) results in all clotting tests compared with a blood sample taken 10–16 hours (trough level) after ingestion of the same dose

What do I do if I suspect an overdose?

Apply the same measures as for patients treated with vitamin K antagonists, excluding vitamin K application. Dialysis is an additional option to eliminate PRADAXA from the blood plasma.[1,2]

	PRADAXA	Warfarin[†]
	**Stop medication** Half life: 12–14 hours*	Half life: **40 hours**
	**Measure** PRADAXA anticoagulation activity with aPTT test	INR
	**Act** Consider hemodialysis because unlike other NOACs, PRADAXA can be dialyzed[1]	Give vitamin K, but it is not enough to reduce the effects of warfarin and can take 24–36 hours to reach maximum effect[1]
	**Additional options[‡]** Blood cells, frozen plasma, thrombocytes, PCC, aPCC and recombinant FVII[§]	

[‡]Based on individual physician decision: There is limited clinical experience to demonstrate the utility of this approach in clinical studies.[1]

* Normal renal function.

† There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of induced thromboembolism is very limited.

§ Recombinant activated factor VII (rFVIIa).

Please see full Summary of Product Characteristics included with this guide.

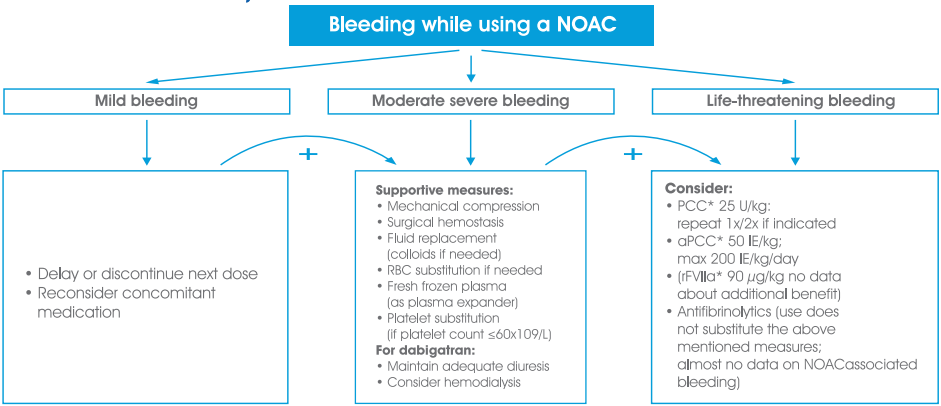
MANAGEMENT OF PATIENTS TREATED WITH PRADAXA IN CASES OF BLEEDING[1]

- Discontinue Pradaxa
- Investigate the source of bleeding
- Oral charcoal application* (if Pradaxa is ingested <2 h before)
- Maintain adequate hemodynamics and diuresis before initiation of standard treatments:

Depending on type/severity of bleeding and vital parameters:

- Surgical hemostasis
- Blood volume replacement (e.g., fresh whole blood or fresh frozen plasma)
- Eliminate Pradaxa via dialysis
- Application of factor concentrates
  - Prothrombin complex concentrates (PCC)* (nonactivated or activated)
  - Recombinant activated factor VIIa (rFVIIa)*
  - Platelet concentrates may be considered when thrombocytopenia is present or long-acting antiplatelet drugs (e.g., acetylsalicylic acid or clopidogrel) have been used

MANAGEMENT OF BLEEDING IN PATIENTS TAKING NOVEL ANTICOAGULANTS BASED ON EXPERT OPINION (EUROPEAN HEART RHYTHM ASSOCIATION)[1,12]



*Use in NOAC-associated bleeding based on only very limited experience in humans.

aPCC: activated prothrombin complex concentrates; PCC: prothrombin complex concentrates; rFVIIa: recombinant Factor VIIa; RBC: red blood cells Each treating physician should determine what medical treatment and/or bleeding management measures should be taken on a case by case basis, based on his/her medical experience and judgment.

Please see full Summary of Product Characteristics included with this guide.

Prescribing Information
PRADAXA® (dabigatran etexilate)

Capsules containing 110 mg or 150 mg dabigatran etexilate (as mesilate) **Action:** Direct thrombin inhibitor **Indication:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as prior stroke, or transient ischaemic attack; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension, 150 mg dabigatran etexilate is also approved for Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Dose and Administration:** Renal function should be assessed by calculating CrCL prior to initiation to exclude patients with severe renal impairment (CrCL < 30 mL/min). Recommended daily dose 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term. In case of intolerability to dabigatran, patients should be instructed to immediately consult their doctor. For SPAF patients aged 80 years or above, or those receiving concomitant verapamil, the recommended daily dose is Pradaxa 220 mg taken as 110 mg twice daily. Pradaxa and verapamil should be taken at the same time. For the following patient groups, the daily dose of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and risk of bleeding: aged 75 – 80 years; with moderate renal impairment (CrCL 30-50 mL/min); with gastritis, oesophagitis or gastroesophageal reflux; other risk of increased bleeding. Close clinical surveillance is recommended in patients with renal impairment. Use is contraindicated in patients with severe renal impairment (CrCL < 30 mL/min). In all patients assess renal function by calculating CrCL prior to initiation to exclude patients with severe renal impairment. Renal function should also be assessed when a decline in renal function is suspected. Additionally in patients > 75 years or with mild to moderate renal impairment, renal function should also be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate. Patients with an increased risk of bleeding: closely monitor clinically looking for signs of bleeding or anaemia. A coagulation test may help identify increased risk patients. No dose adjustment required but close clinical surveillance in patients < 50 kg. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). If switching from Pradaxa to parenteral anticoagulant wait 12 hours after the last dose of Pradaxa; if switching from parenteral anticoagulant to Pradaxa discontinue the parenteral anticoagulant and start Pradaxa 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment; if switching from Pradaxa to VKA adjust the starting time of the VKA based on CrCL; if switching from VKA to Pradaxa stop VKA and give Pradaxa once INR <2.0. Cardioversion patients can stay on Pradaxa whilst being cardioverted. No relevant use of Pradaxa in the paediatric population in the indication. Pradaxa can be taken with or without food. Pradaxa should be swallowed as a whole with a glass of water to facilitate delivery to the stomach. Patients should be instructed not to open the capsule as this may increase the risk of bleeding. **Contraindications:** Hypersensitivity to any component; severe renal impairment (CrCL < 30 mL/min); active clinically significant bleeding; lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, dronedarone; prosthetic heart valves requiring anticoagulant treatment. Warnings and Precautions: Not recommended if liver enzymes > 2 ULN. Haemorrhagic risk: Close clinical surveillance (signs of bleeding or anaemia) is recommended throughout the treatment period, especially when haemorrhagic risk is increased or risk factors combined. Factors which may increase haemorrhagic risk: age ≥ 75 years; moderate renal impairment (CrCL 30 – 50 mL/min); P-glycoprotein inhibitor comedication; body weight < 50 kg; acetylsalicylic acid (aspirin); NSAID; clopidogrel; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); other drugs which may impair haemostasis; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional plateletdefects, recent biopsy, major trauma, bacterial endocarditis, oesophagitis, gastritis or gastroesophageal reflux.

Concomitant use of ticagrelor. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. If severe bleeding occurs, discontinue treatment and investigate the source of the bleeding. Avoid or use with caution medicinal products which may increase the risk of haemorrhage. The use of fibrinolytic medicinal products for the treatment of acute ischaemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range. Avoid concomitant administration with P-gp inducers. Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate; prescribers should consult the Summary of Product Characteristics for further information. Procedures such as spinal anaesthesia may require complete haemostatic function. The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate; these patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma. Treat with caution patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events. Myocardial infarction. Contains Sunset Yellow (E110) which may cause allergic reactions. Interactions: Anticoagulants and antiplatelet aggregation medicinal products; P-gp inhibitors e.g. amiodarone, quinidine, veraparnil, clarithromycin, ticagrelor co-administration (close clinical surveillance); verapamil co-administration - reduce Pradaxa dose to 220 mg (see above) close clinical surveillance is recommended; caution when co-administered with posaconazole; not recommended for concomitant treatment tacrolimus, protease inhibitors including ritonavir and its combinations with other protease inhibitors; avoid with P-gp inducers e.g. rifampicin, St John's wort, carbamazepine, phenytoin; SSRIs or SNRIs. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazoleand other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Ranitidine administration tog ether with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran. **Fertility, pregnancy and lactation:** Avoid pregnancy during treatment. Do not use in pregnancy unless clearly necessary. Discontinue breast-feeding during treatment. **Undesirable effects:** Most commonly reported adverse reactions are bleedings occurring in total in approximately 16.6 % in patients with atrial fibrillation treated for the prevention of stroke and SEE. Common (≥ 1/100 to <1/10): anaemia; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; skin haemorrhage; genitourological haemorrhage, including haematuria. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Legal category POM MA numbers:** 110 mg EU/1/08/442/006 (30 capsules) 150 mg EU/1/08/442/011 (60 capsules) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Str. 173, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in February 2015**