PRADAXA®▼ (DABIGATRAN ETEXILATE)

PRESCRIBER GUIDE FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

This guide provides recommendations for the use of Pradaxa® (dabigatran etexilate) in order to minimize the risk of bleeding, including:

- Indication
- Dosing
- Special patient populations
- Coagulation tests and their interpretation
- Actions to take in overdosing situations

Pradaxa® Patient Alert Card

All patients should be provided with a Patient Alert Card and be counselled about:

- Signs or symptoms of bleeding and when to seek attention from a Healthcare Professional (HCP)
- Importance of treatment compliance
- To carry the Alert Card with them at all times
- The need to inform a HCP that they are taking Pradaxa® if they need to have any surgery or invasive procedure

To order copies of the patient alert card, please go to www.pradaxa.co.uk/educationalpack

Indication[1,2]

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

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

Dosing[1,2]

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

Special patient populations with a reduced daily dose:

- Patients aged 80 years or above should be treated with a daily dose of 220mg taken as one 110mg capsule twice daily.
- Patients between 75-80 years should be treated with a daily dose of 300mg taken as one 150mg capsule twice daily. A dose of 220mg taken as one 110mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.
- In patients who receive dabigatran etexilate concomitantly with verapamil, dosing should be reduced to 220mg taken as one 110mg capsule twice daily.
- For patients with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220mg given as one 110mg capsule twice daily may be considered.
- For patients with moderate renal impairment (creatinine clearance (CrCL) 30-50ml/min), the recommended dose of Pradaxa® is also 300mg taken as one 150mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of Pradaxa® to 220mg taken as one 110mg capsule twice daily should be considered. Treatment with Pradaxa® in patients with severe renal impairment (CrCL < 30ml/min) is contraindicated.

Special patient populations potentially at higher risk of bleeding[1,2]

Patients with an increased bleeding risk (see table 1) should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test (see section on 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 bleed, a dose of 220mg given as one 110mg 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 haemoglobin 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* (below) summarises factors which may increase the haemorrhagic risk.

Pharmacodynamic and kinetic factors	Age ≥75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL)† • P-gp† inhibitor comedication Minor: • Low body weight (<50 kg)
Pharmacodynamic interactions	• Aspirin • NSAID • Clopidogrel
Diseases/procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative GI disease • Recent GI bleeding • Recent biopsy or major trauma • Recent ICH† • Brain, spinal, or ophthalmic surgery • Bacterial endocarditis

†CrCL: Creatinine clearance; P-gp: P-glycoprotein; ICH: intracranial hemorrhage

*For special patient populations requiring a reduced dose, see the "Dosing" section.

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®.

Preoperative phase

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

Table 2 below summarises discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in 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. Any 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.

Coagulation tests and their interpretation[3]

Pradaxa® treatment does not need routine clinical monitoring, neither for short-term nor for long-term treatment. 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 of a patient treated with Pradaxa®. There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. The following tests may serve to assess the risk of bleeding (see Figure 1).

- **Activated partial thromboplastin time (aPTT)** test may be useful in qualitatively determining an excess of anticoagulant activity, however aPTT is less sensitive at high plasma concentrations of dabigatran.[1-3] **Please note:** in the first 2–3 days after surgery, there may be greater test variability therefore results should be interpreted with caution.[3,4]
  - An aPTT >80 seconds at trough (when the next dose is due) is associated with a higher risk of bleeding.[7]

- The actual **Thrombin Time (TT)** test measure will depend on the coagulometer and the thrombin lot used for the measurement. It is therefore advisable to use the **calibrated Hemoclot® Thrombin Inhibitor assay**[5] (a diluted TT assay) with dabigatran standards to calculate the dabigatran concentration rather than to determine TT.[3]
  - A TT measure[1,2] with the **calibrated Hemoclot® thrombin inhibitor assay**[5] (Hyphen BioMed, Neuville-sur-Oise, France) of **>200ng/mL dabigatran plasma concentration** (approximately >65 seconds) prior to the next drug intake after 150mg twice-daily dosing (trough measure, i.e., 10-16 hours after the previous dose) is associated with a higher risk of bleeding.[7]
  - A normal TT measurement indicates no clinically relevant anticoagulant effect of dabigatran.
- **Ecarin Clotting Time (ECT)** provides a direct measure of the activity of direct thrombin inhibitors.[3]
  - **Approximately 3-4 times elevated ECT compared with normal levels prior to the next drug intake** of Pradaxa® (at trough) is associated with a higher risk of bleeding.[7]
- **Prothrombin time (INR)** is not sufficiently sensitive and cannot be recommended.[3]
- **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 (see Figure 1 which illustrates the situation after a single dose of dabigatran etexilate [Pradaxa®]).

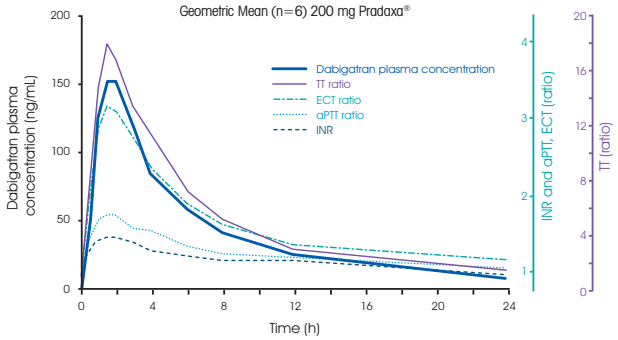

Figure 1. Example of correlation of coagulation parameters with dabigatran clearance of a 200-mg dose. Diagram taken from reference 6.

Please note: To assess the risk of bleeding, qualitative tests may be used such as aPTT, ECT or TT other than the dabigatran calibrated Hemoclot® thrombin inhibitor assay. For a quantitative measurement of dabigatran plasma concentrations, only the dabigatran calibrated Hemoclot® thrombin inhibitor assay is available.[5]

Recommendations for cases of overdose[1-3]

Doses of Pradaxa® beyond those recommended expose the patient to an increased risk of bleeding. In cases where overdose is suspected, coagulation tests may help to determine bleeding risk. Excessive anticoagulation may require discontinuation of Pradaxa®. There is currently no specific antidote to dabigatran. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies. In the event of hemorrhagic 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 standard treatment, e.g., surgical hemostasis and blood volume replacement, should be undertaken at the prescriber's discretion. Consideration may be given to the use of fresh whole blood or fresh frozen plasma. **There is some experimental evidence** to support the role of agents such as activated prothrombin complex concentrates (e.g., FEIBA), recombinant Factor VII a or concentrates of coagulation factors II, IX or X in reversing the anticoagulant activity of dabigatran.[3] **The usefulness in clinical settings has not yet been systematically demonstrated.**[3] Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.[8] All symptomatic treatment has to be given according to the physician's judgement.

References:

1. Boehringer Ingelheim. Pradaxa® 150mg SPC. 2011.
2. Boehringer Ingelheim. Pradaxa® 110mg SPC. 2011.
3. van Ryn J et al. Thromb Haemost 2010; 103:1116–1127.
4. Liesenfeld K-H et al. Br J Clin Pharmacol 2006; 62:527–537.
5. Hemoclot® thrombin inhibitor assay (Quadratech Diagnostics Ltd). Available at www.quadratech.co.uk.
6. Stangier J et al. Br J Clin Pharmacol 2007; 64:292–303.
7. Data on file –DBG 11–05. Boehringer Ingelheim.
8. Guidelines for the use of platelet transfusions. Br J Haem 2003; 122:10-23

This prescriber guide does not substitute the Pradaxa® Summary of Product Characteristics (SmPC).

The recommendations given in this prescriber guide only refer to the use of Pradaxa® in the indication of stroke prevention in atrial fibrillation with twice daily dosing.

Prescribing Information (SPAF – UK) 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 nonvalvular atrial fibrillation with one or more of the following risk factors: 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 **Dose and Administration:** 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. Elderly: Aged ≥ 80 years 220 mg taken as one 110 mg capsule twice daily; 75 – 80 years consider 220 mg taken as one 110 mg capsule twice daily. Patients with an increased risk of bleeding should be closely monitored clinically looking for signs of bleeding or anaemia. Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test may help identify increased risk patients. Patients with gastritis, esophagitis, or gastroesophageal reflux consider 220 mg taken as one 110 mg capsule twice daily due to the elevated risk of major gastro-intestinal bleeding. Patients with renal impairment and a high risk of bleeding consider 220 mg taken as one 110 mg capsule twice daily. Close clinical surveillance is recommended in patients with renal impairment. Pradaxa is contraindicated in severe renal impairment (CrCL < 30 ml/min). Concomitant verapamil 220 mg taken as one 110 mg capsule twice daily; Pradaxa and verapamil should be taken at the same time. 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 anticoagulants to Pradaxa then Pradaxa should be given 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. Not recommended aged < 18 years. Pradaxa should be swallowed whole with water, with or without food. 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; organic lesion at risk of bleeding; impairment of haemostasis; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, tacrolimus. **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 co-medication; body weight < 50 kg; acetylsalicylic acid (aspirin); NSAID; clopidogrel; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative GI disease, recent GI bleeding, recent biopsy or majortrauma, recent ICH or brain, spinal or ophthalmic surgery, bacterial endocarditis. 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 agents which may increase the risk of haemorrhage. 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 agents; Strong P-gp inhibitors e.g. amiodarone, quinidine, verapamil, clarithromycin co-administration (close clinical surveillance); verapamil co-administration - reduce Pradaxa dose to 220 mg (see above); not recommended for concomitant treatment posaconazole, dronedarone, 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. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Ranitidine administration together 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 16.5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE. Common (≥ 1/100, <1/10): anaemia; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; genitourological haemorrhage (150 mg). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 110mg 60 capsules £75.60 150 mg 60 capsules £75.60 **Legal category** POM **MA numbers:** 110mg EU/1/08/442/007 (60 capsules) 150 mg EU/1/08/442/011 (60 capsules) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** July 2011.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

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