# 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 minimise the risk of bleeding, including:

- Indication
- Contraindications
- Dosing
- Special patient populations
- Coagulation tests and their interpretation
- Actions to take in overdose 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/SPAEducationalpack

## Indication[1,2]

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 (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

## Contraindications[1,2]

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCL <30mL/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 anticoagulant agent 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

*continued overleaf*

- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone
- Prosthetic heart valves requiring anticoagulant treatment

## 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, oesophagitis, 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 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

**In all patients:**

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

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

For creatinine in µmol/L:

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

This method is recommended when assessing patients' creatinine clearance prior to and during Pradaxa® treatment.

### Switching

*Pradaxa® treatment to parenteral anticoagulant*

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

*Parenteral anticoagulants to Pradaxa®*

Discontinue the parenteral anticoagulant and start dabigatran etexilate 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)).

*Pradaxa® treatment to Vitamin K antagonists (VKA)*

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

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

Because Pradaxa® can increase 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.

*VKA to Pradaxa®*

The VKA should be stopped. Dabigatran etexilate can be given as soon as the International Normalized Ratio (INR) is <2.0.

### Cardioversion

Patients can stay on dabigatran etexilate while being cardioverted.

## 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.

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

Patients with an increased bleeding risk (see table 1 overleaf) 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:<br>• Moderate renal impairment (30-50mL/min CrCL)†<br>• P-gp† inhibitor comedication<br>Minor:<br>• Low body weight (<50kg) |
| Pharmacodynamic interactions | • Aspirin<br>• NSAID<br>• Clopidogrel<br>• SSRIs or SNRIs#<br>• Other drugs which may impair haemostasis |
| Diseases/procedures with special haemorrhagic risks | • Congenital or acquired coagulation disorders<br>• Thrombocytopenia or functional platelet defects<br>• Oesophagitis, gastritis, gastroesophageal reflux<br>• Recent biopsy, major trauma<br>• Bacterial endocarditis |

* 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

## 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.

## Preoperative phase

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.

## Spinal anaesthesia/epidural anaesthesia/ lumbar puncture

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.

## Coagulation tests and their interpretation[3]

Pradaxa® treatment does not need routine clinical monitoring, neither for short-term nor for long-term treatment.[4,6] However, in cases of suspected overdose or in patients treated with Pradaxa® presenting in emergency departments or prior to surgery, 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. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution. The INR test is unreliable in patients on Pradaxa® and false positive INR elevations have been reported. Therefore INR tests should not be performed.

For a quantitative measurement of dabigatran plasma concentrations, only the dabigatran calibrated Hemoclot® thrombin inhibitor assay is available[5]:

- A diluted TT measure[1,2] (dTT) with the **calibrated Hemoclot®[5] thrombin inhibitor assay** (Hyphen BioMed, Neuville-sur-Oise, France) of **>200ng/mL dabigatran plasma concentration** (approximately >65 seconds[7]) 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[1,2]
- A normal dTT measurement indicates no clinical relevant anticoagulant effect of dabigatran

Table 3 shows coagulation test thresholds at trough (i.e. 10-16 hours after previous dose) that may be associated with an increased risk of bleeding. **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]

| 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.

## 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 haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. The initiation of appropriate standard treatment, e.g., surgical haemostasis 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.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited.

**Please note: Coagulation tests may become unreliable following administration of suggested reversing agents. Caution should be exercised when interpreting these tests.**

Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

Depending on local availability, consultation of a coagulation expert should be considered in case of major bleedings.

**References:**


1. Boehringer Ingelheim. Pradaxa® 150mg hard capsules Summary of Product Characteristics.
2. Boehringer Ingelheim. Pradaxa® 110mg hard capsules Summary of Product Characteristics.
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 (Hyphen BioMed, Neuville-sur-Oise, France). Available at www.dabigatrantesting.com
6. Stangier J et al. Br J Clin Pharmacol 2007; 64:292–303.
7. Huisman V et al. Thromb Haemost 2012; 107.


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 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 **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 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 co-medication; 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 platelet defects, 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, verapamil, 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. 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 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. **Pack sizes and NHS price:** *110 mg* 60 capsules £65.90 *150 mg* 60 capsules £65.90 **Legal category** POM **MA numbers:** *110 mg* EU/1/08/442/007 (60 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** June 2014.

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

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