



Prescribing Summary

This is a condensed version of the Product Monograph. For complete information please refer to the Product Monograph available at www.boehringer-ingenheim.ca, or by writing to Boehringer Ingelheim (Canada) Ltd., 5180 South Service Road, Burlington, Ontario, L7L 5H4.



Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Anticoagulant

INDICATIONS AND CLINICAL USE

PRADAX (dabigatran etexilate) is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery.

Geriatrics (>65 years of age): Clinical studies have been conducted in a patient population with a mean age >65 years (see WARNINGS AND PRECAUTIONS, Geriatrics, and Renal; DOSAGE AND ADMINISTRATION, Renal Impairment, and Elderly).

Pediatrics (<18 years of age): The safety and efficacy of PRADAX have not been established in children less than 18 years of age, therefore PRADAX is not recommended in this patient population.

CONTRAINDICATIONS

PRADAX (dabigatran etexilate) is contraindicated in patients with:

- Severe renal impairment (CrCL <30 mL/min);
- Hemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of hemostasis;
- Lesions at risk of clinically significant bleeding, e.g. cerebral infarction (hemorrhagic or ischemic) within the last 6 months;
- Concomitant treatment with strong P-glycoprotein inhibitors, e.g. quinidine (see DRUG INTERACTIONS);
- Known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container.

SPECIAL POPULATIONS

For use in Special Populations, see WARNINGS AND PRECAUTIONS, Special Populations.



Safety Information

WARNINGS AND PRECAUTIONS

The following WARNINGS AND PRECAUTIONS are listed in alphabetical order:

Hematologic

As with all anticoagulants, bleeding may occur. Should severe bleeding occur, treatment with PRADAX must be discontinued and the source of bleeding investigated promptly.

Treatment that should NOT be administered concomitantly with PRADAX due to increase in bleeding risk, includes: unfractionated heparin and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, bivalirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, sulfinpyrazone, and vitamin K antagonists, such as warfarin. Unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.

Acetylsalicylic acid (ASA) at doses of 81 to 325 mg daily has been shown to increase risk of bleeding when given concomitantly with PRADAX at doses above those currently recommended, i.e. above 220 mg daily. Co-administration of low-dose ASA, i.e. ≤160 mg daily with PRADAX has not been adequately studied and is not recommended.

Close observation, e.g. looking for signs of bleeding or anemia, is required in the following situations that may increase the hemorrhagic risk:

- Recent events, including: biopsy or major trauma; cerebral, spinal or ophthalmic surgery;
- Concomitant use of NSAIDs should be undertaken with caution;
- Diseases associated with an increased risk of bleeding, such as congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, history of intracranial hemorrhage or hemorrhagic infarction, bacterial endocarditis.

Hepatic/Biliary/Pancreatic

Patients with moderate or severe hepatic impairment (Child-Pugh classification B and C), or with elevated liver enzymes >2x ULN were excluded from clinical trials. Therefore, PRADAX is not recommended in these patients.

Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture

In patients treated with dabigatran etexilate for VTE prevention following major orthopedic surgery and who undergo spinal or epidural anesthesia, or in whom lumbar puncture is performed in follow-up to surgery, the formation of spinal or epidural hematomas that may result in long-term or permanent paralysis cannot be excluded.

In the case of these peri-spinal procedures, administration of the first dose of PRADAX should occur after hemostasis has been obtained and no sooner than 2 hours following puncture or removal of catheters related to these procedures.

The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other products affecting hemostasis. Accordingly, the use of PRADAX is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters.

Renal

Following oral dosing with dabigatran etexilate, there is a direct correlation of systemic exposure to dabigatran with degree of renal impairment. Severe renal insufficiency (CrCL <30 mL/min) has been shown to increase exposure to dabigatran six-fold (see CONTRAINDICATIONS), while moderate renal impairment (CrCL 30-50 mL/min) increased exposure 2.7-fold. While the standard dose of PRADAX is 220 mg daily for patients with intact renal function, for patients with moderate renal impairment (CrCL 30-50 mL/min), the recommended daily dose is 150 mg daily (see DOSAGE AND ADMINISTRATION, Renal Impairment). PRADAX is contraindicated in cases of severe renal impairment (CrCL <30 mL/min). Patients who develop acute renal failure while on PRADAX should discontinue such treatment.

As dose selection of PRADAX is based on renal function, creatinine clearance should be evaluated before initiating treatment, and during treatment as appropriate (see DOSAGE AND ADMINISTRATION, Renal Impairment).

SPECIAL POPULATIONS

Pregnant Women: Since there are no studies of PRADAX in pregnant women, the potential risk in these patients is unknown. Animal reproductive studies did not show any adverse effects on fertility or postnatal development of the neonate.

Women of child-bearing potential should avoid pregnancy during treatment with PRADAX and when pregnant, women should not be treated with PRADAX unless the expected benefit is greater than the risk.

Nursing Women: Breast-feeding during treatment with PRADAX is not recommended. There are no clinical data available on the excretion of dabigatran into breast milk.

Geriatrics (>65 years of age): In general, patients should be treated with a standard dose of 220 mg PRADAX daily. In patients >75 years of age, PRADAX should be used with caution, and a dose of 150 mg daily should be considered since age-related decrease of renal function is frequently encountered (see WARNINGS AND PRECAUTIONS, Renal). Regardless of age, in patients with moderate renal impairment (CrCL 30-50 mL/min), because of an increased risk of bleeding, the recommended dose of PRADAX is 150 mg daily (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Pediatrics (<18 years of age): The safety and efficacy of PRADAX have not been established in children less than 18 years of age, therefore PRADAX is not recommended in this patient population.

Patients of Low Body Weight (<50 kg): Since limited data are available in these patients, PRADAX should be used with caution.

Monitoring and Laboratory Tests

At recommended doses of PRADAX, dabigatran prolongs the activated partial thromboplastin time (aPTT). In patients who are bleeding due to excess activity of dabigatran, the aPTT test would be expected to be elevated. Both thrombin time (TT) and ecarin clotting time (ECT) may be helpful in assessing anticoagulant activity of dabigatran, if necessary (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). In the therapeutic range, aPTT is less sensitive to anticoagulant activity than either TT or ECT and should not be relied upon (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

ADVERSE REACTION SERIOUSNESS AND INCIDENCE

Adverse Drug Reaction Overview

A total of 10,084 patients were exposed to at least one dose of PRADAX in four active-controlled clinical trials conducted to evaluate the safety and effectiveness of dabigatran etexilate in the prevention of venous thromboembolic events (VTE) following major elective orthopedic surgery. Of these, 5,419 were treated with 150 mg or 220 mg daily of PRADAX, while 389 received doses of less than 150 mg daily, and 1,168 received doses in excess of 220 mg daily.

The adverse reactions that can with reasonable certainty be attributed to dabigatran are those of bleeding or signs of bleeding, e.g. wound bleeding and anemia.

Table 1: Number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the RE-MODEL and RE-NOVATE trials, according to dose

| | Dabigatran etexilate 150 mg N (%) | Dabigatran etexilate 220 mg N (%) | Enoxaparin 40 mg QD N (%) |
|-----------------|-----------------------------------|-----------------------------------|---------------------------|
| Treated | 1866 (100.0) | 1825 (100.0) | 1848 (100.0) |
| Major bleeding* | 24 (1.3) | 33 (1.8) | 27 (1.5) |
| Any bleeding | 258 (13.8) | 251 (13.8) | 247 (13.4) |

* Major bleeding: Major bleeding was defined as clinically overt bleeding associated with ≥ 20 g/L fall in hemoglobin; clinically overt bleeding leading to transfusion of ≥ 2 units packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation. Major bleeding included those events occurring at the surgical site.

Table 2: Number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the RE-MOBILIZE trial, according to dose

| | Dabigatran etexilate 150 mg N (%) | Dabigatran etexilate 220 mg N (%) | Enoxaparin 30 mg BID N (%) |
|-----------------|-----------------------------------|-----------------------------------|----------------------------|
| Treated | 871 (100.0) | 857 (100.0) | 868 (100.0) |
| Major bleeding* | 5 (0.6) | 5 (0.6) | 12 (1.4) |
| Any bleeding | 72 (8.3) | 74 (8.6) | 84 (9.7) |

There were no documented cases of hypersensitivity following oral administration of dabigatran etexilate.

Adverse reactions reported from any treatment group in treated patients of controlled VTE prevention studies were: abnormal liver function tests; anemia; thrombocytopenia; hematoma; wound hemorrhage; hemorrhage; hemoglobin decreased; occult blood positive; blood urine present; hematocrit decreased; wound secretion; post-procedural hematoma; post-procedural hemorrhage; anemia post-operative; traumatic hematoma; post-procedural discharge; incision site hemorrhage; hematuria; hemarthrosis; epistaxis; gastro-intestinal hemorrhage; hemorrhoidal hemorrhage; rectal hemorrhage; ecchymosis; bloody discharge; catheter site hemorrhage; post-procedural drainage; wound drainage; alanine aminotransferase increased; aspartate aminotransferase increased; hepatic enzyme increased; hepatic function abnormal/liver function test abnormal; transaminases increased; alanine aminotransferase increased 3x ULN. Please refer to the Product Monograph for complete information.

DRUG INTERACTIONS

Based on *in vitro* evaluation, neither dabigatran etexilate or its active moiety, dabigatran, were shown to be metabolised by the human cytochrome P450 system, nor did they exhibit effects on human CYP 450 isozymes.

Concomitant use of PRADAX with treatment that acts on hemostasis or coagulation increases bleeding risk (see WARNINGS AND PRECAUTIONS, Hematologic). Co-administration of PRADAX with other anticoagulants or antithrombotic therapy has not been adequately studied and is not recommended.

Drug-Drug Interactions

Transporter Interactions: Dabigatran etexilate, but not dabigatran, is a substrate with moderate affinity for the efflux P-glycoprotein (P-gp) transporter. Therefore potent P-glycoprotein inducers or inhibitors may be expected to impact exposure to dabigatran.

P-glycoprotein Inhibitors: Potent P-gp inhibitors like verapamil and clarithromycin, may be expected to increase systemic exposure to dabigatran. Accordingly, their use is not recommended. The P-glycoprotein inhibitor, quinidine, is contraindicated (see CONTRAINDICATIONS).

P-glycoprotein Inducers: Potent P-gp inducers such as rifampicin and Saint John's Wort may reduce the systemic exposure of dabigatran. Less potent inducers such as tenofovir can potentially reduce systemic exposure. Caution is advised when co-administering these drug products.

P-glycoprotein Substrates: Dabigatran etexilate is not expected to have a clinically meaningful interaction with P-glycoprotein substrates that do not also act as inhibitors or inducers of P-gp.

Summary of Drug-Drug Interactions

The use of PRADAX with quinidine is contraindicated.

Co-administration of PRADAX with antacids should be avoided within 24 hours after surgery.

Caution should be exercised when used with amiodarone, and a dose adjustment to 150 mg daily of PRADAX is recommended.

No dose adjustment of PRADAX is recommended when used with atorvastatin, diclofenac, digoxin, and pantoprazole.

Drug-Food Interactions

Food does not affect the bioavailability of PRADAX but delays the time-to-peak plasma concentrations by 2 hours.

Drug-Herb Interactions

Drug-herb interactions have not been investigated. Potent P-gp inducers such as Saint John's Wort (*Hypericum perforatum*) may be expected to affect systemic exposure of dabigatran. Co-administration of these products is not recommended.

Drug-Laboratory Interactions

No single test (aPTT, INR, TT, ECT) is adequate to reliably assess the anticoagulant activity of dabigatran following PRADAX administration. However, in patients who are bleeding, an aPTT determination with values greater than 2.5x control suggests excessive anticoagulation due to dabigatran. At therapeutic levels of dabigatran, thrombin time (TT) is the best measure of the pharmacodynamic effect of dabigatran because of its linear and sensitive relationship with dabigatran exposure (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). The ecarin clotting test (ECT) may also be useful in these circumstances.

Drug-Lifestyle Interactions

No direct interaction between dabigatran etexilate and alcohol was demonstrated pre-clinically or has been hypothesised. However, excessive use of alcohol may increase the likelihood of personal injury and should be avoided in patients taking any systemic anticoagulant, including PRADAX.

The effect of PRADAX on the ability to drive and use machines has not been investigated.

To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at 1-866-234-2345 or contact: Boehringer Ingelheim Canada Ltd., 5180 South Service Road, Burlington, Ontario, L7L 5H4.



Administration

Recommended Dose and Dosage Adjustment

VTE prevention following elective knee replacement surgery: The recommended dose of PRADAX is 220 mg once daily taken orally as 2 capsules of 110 mg in patients with intact renal function. Treatment should normally be initiated within 1-4 hours of completed surgery once hemostasis is secured. Start with a single capsule of 110 mg, and continue with 2 capsules once daily thereafter for a total of 10 days. If hemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery for whatever reason, then treatment should be initiated with 2 capsules at once.

VTE prevention following elective hip replacement surgery: The recommended dose of PRADAX is 220 mg once daily taken orally as 2 capsules of 110 mg in patients with intact renal function. Treatment should normally be initiated within 1-4 hours of completed surgery once hemostasis is secured. Start with a single capsule of 110 mg, and continue with 2 capsules once daily thereafter for a total of 28-35 days. If hemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery for whatever reason, then treatment should be initiated with 2 capsules at once.

Renal Impairment: Following oral dosing with dabigatran etexilate, there is a direct correlation of systemic exposure to dabigatran with degree of renal impairment (see WARNINGS AND PRECAUTIONS, Renal). The kidneys account for 85% of dabigatran clearance.

Patients with moderate renal impairment (CrCL 30-50 mL/min) exposed to dabigatran etexilate appear to be at higher risk of bleeding. Accordingly, treatment with PRADAX should be initiated orally in these patients within 1-4 hours of completed surgery once hemostasis is secured. Start with 75 mg taken as a single capsule, and continued at 150 mg, taken as 2 capsules of 75 mg once daily thereafter.

There are no data to support use in patients with severe renal impairment (creatinine clearance <30 mL/min). Given the substantial increase in dabigatran exposure observed in this patient population, treatment with PRADAX is not recommended (see CONTRAINDICATIONS, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

Creatinine clearance can be estimated using the Cockcroft-Gault formula as follows:

Creatinine clearance (mL/min) =

$$\begin{aligned} \text{Males:} & \quad \frac{(140 - \text{age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}} \\ \text{Females:} & \quad \frac{0.85 \times (140 - \text{age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}} \end{aligned}$$

Hepatic Impairment: Patients with moderate and severe hepatic impairment were excluded from clinical trials. Therefore, the use of PRADAX is not recommended in this population.

Elderly: In patients >75 years of age, PRADAX should be used with caution, and a dose of 150 mg daily should be considered, taken as 2 capsules of 75 mg daily, since age-related compromise of renal function is frequently encountered (see WARNINGS AND PRECAUTIONS, Geriatrics, and Renal).

Children: Since PRADAX has not been investigated in patients <18 years of age, treatment is not recommended.

Patient Body Weight: Population PK modelling shows that patients with a body weight of about 120 kg have about 20% lower drug exposure. Patients with a body weight of about 48 kg have about 25% higher drug exposure compared to patients with average weight.

Switching From PRADAX Treatment to Parenteral Anticoagulant: Wait 24 hours after the last dose of dabigatran etexilate before switching to a parenteral anticoagulant.

Switching From Parenteral Anticoagulants Treatment to PRADAX: No data are available, therefore it is not recommended to start the administration of dabigatran etexilate before the next scheduled dose of the parenteral anticoagulant would have been due.

Missed Dose

Patients should be advised that if a dose is missed, they should not take a double dose.

Administration

PRADAX can be taken with food, or on an empty stomach with water.

SUPPLEMENTAL PRODUCT INFORMATION

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 3: Common adverse reactions observed in ≥1% of dabigatran-treated patients in active-controlled VTE prevention trials

| | Dabigatran etexilate 150 mg N (%) | Dabigatran etexilate 220 mg N (%) | Enoxaparin N (%) |
|---|-----------------------------------|-----------------------------------|-----------------------|
| | 2737 (100) | 2682 (100) | 3181 (100) |
| Blood and lymphatic system | | | |
| Anemia | 110 (4.0) | 117 (4.4) | 141 (4.5) |
| Gastrointestinal hemorrhage | 33 (1.2) | 17 (0.6) | 20 (0.6) ^a |
| Hematuria | 34 (1.2) | 31 (1.2) | 25 (0.8) |
| Vascular disorders | | | |
| Hematoma | 38 (1.4) | 37 (1.4) | 55 (1.8) |
| Wound hemorrhage | 35 (1.3) | 28 (1.0) | 31 (1.0) |
| Investigations | | | |
| Hemoglobin decreased | 45 (1.6) | 35 (1.3) | 74 (2.4) |
| Injury, poisoning and procedural complications | | | |
| Wound secretion | 130 (4.7) | 130 (4.8) | 93 (3.0) |
| Post-procedural hematoma | 66 (2.4) | 45 (1.7) | 78 (2.5) |
| Post-procedural hemorrhage | 28 (1.5) | 43 (2.4) | 32 (1.7) |
| Anemia post-operative | 37 (1.4) | 54 (2.0) | 56 (1.8) |
| Traumatic hematoma | 37 (1.4) | 41 (1.5) | 51 (1.6) |
| Post-procedural discharge | 31 (1.1) | 34 (1.3) | 31 (1.0) |
| Laboratory investigations | | | |
| ALT ≥3x ULN | 68 (2.5) | 58 (2.2) | 95 (3.5) ^b |

^a Based on N=3108

^b Based on N=2716

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Observed with exposure to dabigatran 150 mg and 220 mg during active-controlled venothromboembolic prevention trials in the context of major orthopedic surgery:

Blood and lymphatic system: thrombocytopenia

Gastrointestinal disorders: hemorrhoidal hemorrhage, rectal hemorrhage

General: bloody discharge, catheter site hemorrhage

Hepatobiliary disorders: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatic function abnormal/liver function test abnormal, transaminases increased

Injury, poisoning and procedural complications: incision site hemorrhage

Investigations: occult blood positive, blood urine present, hematocrit decrease

Musculoskeletal and cumulative tissue disorders: hemarthrosis

Respiratory and thoracic system: epistaxis

Skin and sub-cutaneous tissue: ecchymosis

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

Vascular disorders: hemorrhage

Table 4: Summary of drug-drug interactions

| Proper name | Ref* | Effect | Clinical comment |
|--|------|---|---|
| Amiodarone | CT | When dabigatran etexilate was co-administered with amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. Dabigatran AUC and C _{max} were increased by about 60% and 50%, respectively. | Adjust dosing to 150 mg daily PRADAX with amiodarone. Caution should be exercised. |
| Antacids (aluminium compounds, sodium bicarbonate, calcium and/or magnesium compounds, or combinations of these) | CT | In population PK analyses, a reduction in dabigatran exposure by 35% was seen over the first 24 hours following surgery. Thereafter, (>24 hours after surgery), a reduction of about 11% was observed. | Diminished clinical effect may occur. Co-administration with PRADAX should be avoided within 24 hours after surgery. |
| Atorvastatin | CT | When dabigatran etexilate was co-administered with atorvastatin, exposure of atorvastatin, atorvastatin metabolites was not significantly changed. Dabigatran concentrations were decreased about 20%. | No dose adjustment is recommended. |
| Diclofenac | CT | When dabigatran etexilate was co-administered with diclofenac, pharmacokinetics of both drugs appeared unchanged. | No dose adjustment is recommended. |
| Digoxin | CT | When dabigatran etexilate was co-administered with digoxin, no PK-interaction was observed. | No dose adjustment is recommended. |
| Pantoprazole | CT | When dabigatran etexilate was co-administered with pantoprazole, a decrease in dabigatran AUC of about 30% was observed. | No dose adjustment is recommended. Diminished clinical effect may occur. |
| Quinidine | CT | When dabigatran etexilate was co-administered with 600 mg quinidine sulfate, the exposure to dabigatran was approximately twice expected, based on the limited data set (n=3 female subjects who received co-administration). | Co-administration with PRADAX is contraindicated. |

* C=Case Study; CT=Clinical Trial; T=Theoretical

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no antidote to dabigatran etexilate or dabigatran. Doses of PRADAX beyond those recommended expose the patient to increased risk of bleeding. 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 treatment, e.g. surgical hemostasis or the transfusion of fresh frozen plasma, should be undertaken. Dabigatran can be dialysed, although there is no clinical experience to demonstrate the utility of this approach.

Product monograph is available upon request or at www.boehringer-ingenheim.ca

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