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- Title and Running Title (you may copy and paste these from your manuscript) YOUR TITLE MUST BE UNDER 80 CHARACTERS (including spaces)

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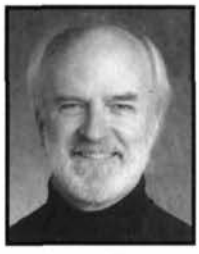

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Pr Pradax™
dabigatran etexilate

Dabigatran Etexilate 110mg and 150mg Capsules

Prescribing Summary

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

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION:
Anticoagulant

INDICATIONS AND CLINICAL USE

- Prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

Geriatrics (>65 years of age): Clinical studies have been conducted in patients with a mean age >65 years. Safety and efficacy data are available (see CLINICAL TRIALS in the Product Monograph).
Pharmacokinetic studies in older subjects demonstrate an increase in exposure to dabigatran in most of those patients, usually in association with age-related decline of renal function (see WARNINGS AND PRECAUTIONS, Renal, and 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.

CONTRAINDICATIONS

- Severe renal impairment (CrCl <30mL/min)
- Hemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of hemostasis
- Lesions at risk of clinically significant bleeding, e.g., extensive cerebral infarction (hemorrhagic or ischemic) within the last 6 months, or active peptic ulcer disease with recent bleeding
- Concomitant treatment with strong P-glycoprotein (P-gp) inhibitors, i.e., oral ketoconazole (see DRUG INTERACTIONS)
- Known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

Safety Information

WARNINGS AND PRECAUTIONS
The following Warnings and Precautions are listed in alphabetical order.

Bleeding
As with all anticoagulants, PRADAX should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with PRADAX. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed PRADAX (see CONTRAINDICATIONS).
Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially if risk factors are combined.

Table 1: Factors which increase hemorrhagic risk, as identified in clinical studies

Factors increasing dabigatran plasma levels	Moderate renal impairment (30-50 mL/min CrCl)
	P-glycoprotein-inhibitor comedication
Pharmacodynamic interactions	Acetylsalicylic acid
	NSAID
	Clopidogrel
Diseases/procedures with special hemorrhagic risks	Congenital or acquired coagulation disorders
	Thrombocytopenia or functional platelet defects
	Active ulcerative gastrointestinal disease
	Recent gastro-intestinal bleeding
	Recent biopsy or major trauma
	Recent intracranial hemorrhage
	Brain, spinal or ophthalmic surgery
	Bacterial endocarditis
Others	Age ≥75 years

The measurement of dabigatran-related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.
In patients who are bleeding, an aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT >80 sec at trough, i.e., when the next dose is due, is associated with a higher risk of bleeding (see Monitoring and Laboratory Tests).
Should severe bleeding occur, treatment with PRADAX must be discontinued and the source of bleeding investigated promptly.
Agents that may enhance the risk of hemorrhage should not be administered concomitantly with PRADAX, or, if necessary, should only be administered with caution (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions in the Product Monograph).
Treatments that should NOT be administered concomitantly with PRADAX due to increase in bleeding risk include: unfractionated heparin and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, bivalirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, sulfinpyrazone, and vitamin K antagonists such as warfarin.
The concomitant use of PRADAX with the following treatments has not been studied and may increase the risk of bleeding: rivaroxaban, prasugrel, and the strong P-gp inhibitors itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.
Unfractionated heparin may be administered at doses necessary to maintain a patent central venous or arterial catheter.
In patients with atrial fibrillation treated for the prevention of stroke and systemic embolism, the co-administration of oral anti-platelet (including aspirin and clopidogrel) and NSAID therapies increases the risk of bleeding by about two-fold (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph). If necessary, co-administration of low-dose ASA, i.e., ≤100 mg daily with PRADAX may be considered for other indications than stroke prevention in atrial fibrillation. Note that in the RELY trial, there is no evidence that the addition of ASA or clopidogrel to dabigatran, or its comparator warfarin, improved outcomes in respect to stroke (see CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation in the Product Monograph).
Treatment initiation with verapamil should be avoided in patients following orthopedic surgery who are already treated with PRADAX. Simultaneous initiation of treatment with PRADAX and verapamil should also be avoided at any time (see DRUG INTERACTIONS, *P-glycoprotein inhibitors*).

Interaction with P-gp inducers
The concomitant use of PRADAX with the strong P-gp inducer, rifampicin, reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see DRUG INTERACTIONS and Special Populations).

Surgery/Procedural Interventions
Patients on PRADAX who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of PRADAX may be required.

Pre-operative Phase
In advance of invasive or surgical procedures PRADAX should be stopped temporarily due to an increased risk of bleeding. If possible, PRADAX should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding (see DOSAGE AND ADMINISTRATION) or in major surgery where

complete hemostasis may be required, consider stopping PRADAX 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer (see DOSAGE AND ADMINISTRATION, Renal). This should be considered in advance of any procedures.

PRADAX is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min). Should acute renal failure occur before surgery is required, PRADAX should generally be stopped at least 5 days before major surgery.

If acute intervention is required, PRADAX should be temporarily discontinued, due to increased risk of bleeding. Surgery or procedural interventions should be delayed if possible until at least 12 hours after the last dose of PRADAX, with risk of bleeding weighed against the urgency of the needed intervention.

Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture

Procedures such as spinal anesthesia may require complete hemostatic function.

In patients treated with PRADAX 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.

Post-Procedural Period

Resume treatment with PRADAX as soon as complete hemostasis is achieved.

Renal

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.

- *Patients with atrial fibrillation treated for prevention of stroke and systemic embolism:* Since no dose adjustment is necessary for most atrial fibrillation patients with moderate renal impairment (CrCl 30-50 mL/min), a standard daily dose of 300 mg, taken orally as one 150 mg capsule twice daily is recommended (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):

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure; especially in those patients with age-related decline of renal function (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Renal Impairment).

- *Patients with atrial fibrillation treated for prevention of stroke and systemic embolism:* Patients aged 80 years and above should be treated with a daily dose of 220 mg taken orally as one 110 mg capsule twice daily. This alternate dosing may also be considered for other geriatric patients (see DOSAGE AND ADMINISTRATION, Elderly). Use with caution.

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 coagulation time as measured by the activated partial thromboplastin time (aPTT), thrombin time (TT) and ecarin clotting time (ECT). In patients who are bleeding due to excess activity of dabigatran, these coagulation tests would be expected to be elevated and may be helpful in assessing anticoagulant activity of dabigatran, if necessary (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics in the Product Monograph). The aPTT is generally less sensitive to anticoagulant activity than either TT or ECT (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

However, the aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec at trough (when the next dose is due) is associated with a higher risk of bleeding. In circumstances where there is no excess of anticoagulant activity, the utility of aPTT is limited in monitoring anticoagulant status of patients taking PRADAX.

ADVERSE REACTIONS

The safety of PRADAX has been evaluated overall in 22,126 patients.

A total of 10,084 patients were exposed to at least one dose of dabigatran as study medication 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.

In the RELY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation, a total of 12,042 patients were exposed to PRADAX. Of these, 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily.

About 21% of patients with atrial fibrillation treated with dabigatran and about 16% of patients treated with warfarin for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse events considered related to treatment.

Bleeding

Bleeding is the most relevant side effect of PRADAX. Bleeding of any type or severity occurred in approximately 14% of patients treated short-term for elective hip or knee replacement surgery and in long-term treatment in 16.5% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

A summary description of major and total bleeding is provided in Table 2.

Table 2 shows the number of patients experiencing major and total bleeding event rates during the treatment period in the RELY study, conducted in patients with atrial fibrillation. In Table 2, the category of major bleeds includes both life-threatening and non-life threatening bleeds. Within life-threatening, intracranial bleeds is a subcategory of life-threatening bleeds.

Intracranial bleeds include intracerebral (hemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.

Table 2: Frequency and annualized event rate (%) of bleeding events from the RELY trial

	Dabigatran etexilate 110 mg bid N (%)	Dabigatran etexilate 150 mg bid N (%)	Warfarin** N (%)
Patients randomized	6,015	6,076	6,022
Patient-years	11,899	12,033	11,794
Major bleeding event (MBE)*	342 (2.9)	399 (3.3)	421 (3.6)
Hazard ratio vs. warfarin (95% CI)	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	
p-value	0.0026	0.3146	
Life threatening MBE	147 (1.2)	179 (1.5)	218 (1.9)
Hazard ratio vs. warfarin (95% CI)	0.67 (0.54, 0.82)	0.80 (0.66, 0.98)	
p-value	0.0001	0.0305	
Intra-cranial hemorrhage (ICH)*	27 (0.2)	38 (0.3)	90 (0.8)
Hazard ratio vs. warfarin (95% CI)	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	
p-value	< 0.0001	< 0.0001	
Any bleeding event†	1,754 (14.7)	1,993 (16.6)	2,166 (18.4)
Hazard ratio vs. warfarin (95% CI)	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	
p-value	< 0.0001	0.0016	

*Adjudicated bleeds
**Dose-adjusted warfarin to an INR of 2.0 – 3.0
*ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.
†Investigator-reported bleeding events

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in hemoglobin of at least 20 grams per litre or leading to a transfusion of at least 2 units of blood or packed cells;
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:

- Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of at least 50 grams per litre; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

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 with atrial fibrillation in the active- controlled trial, RELY

	Dabigatran etexilate 110 mg N (%)	Dabigatran etexilate 150 mg N (%)	Warfarin N (%)
	5,983 (100)	6,059 (100)	5,998 (100)
Bleeding and anemia*	**599 (10.0)**	**747 (12.3)**	**825 (13.8)**
Anemia	73 (1.2)	97 (1.6)	74 (1.2)
Epistaxis	66 (1.1)	67 (1.1)	107 (1.8)
Gastrointestinal hemorrhage	196 (3.3)	277 (4.6)	155 (2.6)
Urogenital hemorrhage	66 (1.1)	84 (1.4)	96 (1.6)
Gastrointestinal disorders*	**735 (12.3)**	**772 (12.7)**	**220 (3.7)**
Abdominal pain	135 (2.3)	134 (2.2)	15 (0.3)
Diarrhea	75 (1.3)	71 (1.2)	11 (0.2)
Dyspepsia	250 (4.2)	234 (3.9)	13 (0.2)
Nausea	58 (1.0)	73 (1.2)	12 (0.2)

*Aggregate incidence presented for all adverse reactions within the body system, including those reactions occurring <1% and not listed in the Table above.Gastrointestinal adverse reactions occurred more often with dabigatran etexilate than warfarin. These were related to dyspepsia (including upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort), or gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic *gastritis, hemorrhagic erosive gastritis, gastrointestinal ulcer*).
Gastrointestinal (GI) hemorrhage occurred at a higher frequency with PRADAX compared to warfarin (see Table 3). GI adjudicated major bleeds were reported at 1.1%, 1.6%, and 1.1% (annualized rates) in the DE 110 mg, DE 150 mg and warfarin groups, respectively. GI life-threatening bleeds occurred with a frequency of 0.6%, 0.8% and 0.5% in the DE 110 mg, DE 150 mg and warfarin groups, respectively. Any GI bleeds occurred with a frequency of 5.4%, 6.1% and 4.0% in the DE 110 mg, DE 150 mg and warfarin groups, respectively. The underlying mechanism of the increased rate of GI bleeding has not been established (see CLINICAL TRIALS, Prevention of stroke and systemic embolism in patients with atrial fibrillation in the Product Monograph).
Allergic reactions or drug hypersensitivity including urticaria, bronchospasm, rash and pruritus have been reported in patients who received dabigatran etexilate. Rare cases of anaphylactic reactions have also been reported.

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

Observed with exposure to dabigatran 110 mg bid and 150 mg bid during the RELY trial, an active-controlled clinical trial for the prevention of stroke and systemic embolism in patients with atrial fibrillation:

Blood and lymphatic system disorders: thrombocytopenia
Vascular disorders: hematoma, hemorrhage
Gastrointestinal disorders: gastrointestinal ulcer, gastroesophagitis, gastro-esophageal reflux disease, vomiting, dysphagia
Hepatobiliary disorders: hepatic function abnormal/liver function test abnormal, hepatic enzyme increased
Skin and subcutaneous tissue disorders: skin hemorrhage, urticaria, rash, pruritus
Musculoskeletal and connective tissue and bone disorders: hemarthrosis
Renal and urinary disorders: hematuria
General disorders and administration site conditions: injection site hemorrhage, catheter site hemorrhage
Injury, poisoning and procedural complications: incision site hematoma, traumatic hematoma, incision site hemorrhage
Immune system disorder: drug hypersensitivity
Respiratory disorders: hemoptysis, bronchospasm
Nervous system disorders: intracranial hemorrhage

For abnormal liver function tests reported in the RE-LY trial, please see Table 5.
To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at 1-866-234-2345, or contact: Boehringer Ingelheim (Canada) Ltd., Drug Safety at 1-800-263-5103 ext. 4603.

DRUG INTERACTIONS

Based on *in vitro* evaluation, neither dabigatran etexilate nor its active moiety, dabigatran, have been shown to be metabolized by the human cytochrome P450 system, nor did they exhibit effects on human CYP P450 isozymes. Concomitant use of PRADAX with treatments that interfere with hemostasis or coagulation increases bleeding risk (see WARNINGS AND PRECAUTIONS, Bleeding). Co-administration of PRADAX with other anticoagulants has not been adequately studied and is not recommended.
In the RELY trial, conducted in patients with atrial fibrillation, a two-fold increase in major bleeding was seen in both dabigatran study treatment arms, as well as that of the comparator, warfarin, when ASA was administered concomitantly (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph; CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation in the Product Monograph; and DOSAGE AND ADMINISTRATION).

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: P-gp inhibitors like verapamil, quinidine and amiodarone may be expected to increase systemic exposure to dabigatran, see Table 4 below. The strong P-glycoprotein inhibitor ketoconazole, when administered orally, is contraindicated (see CONTRAINDICATIONS). If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anemia), along with a sense of caution is required when dabigatran is co-administered with strong P-glycoprotein inhibitors.
P-glycoprotein inducers: The concomitant use of PRADAX with the strong P-gp inducer rifampicin, reduces dabigatran plasma concentration. Other P-gp inducers such as carbamazepine and St John's Wort are also expected to 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.

Table 4: Summary of Drug-Drug Interactions

Proper name	Ref*	Effect	Clinical comment
Amiodarone	CT	Dabigatran exposure in healthy subjects was increased by 60% in the presence of amiodarone (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph).	Adjust dosing for patients treated for prevention of VTE after hip- or knee-replacement surgery to 150 mg daily PRADAX with amiodarone. Caution should be exercised.
			No dose adjustment is generally recommended for AF patients. Use with caution. Occasional testing of aPTT may be considered to rule out excessive anticoagulant effect.
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, as may be expected for any drug resulting in an increase in gastric pH during PRADAX administration. PRADAX should be administered at least 2 hours before taking an antacid. Co-administration with PRADAX should be avoided within 24 hours after orthopedic surgery.
Atorvastatin	CT	When dabigatran etexilate was co-administered with atorvastatin, exposure of atorvastatin, and atorvastatin metabolites were not significantly changed. Dabigatran concentrations were decreased about 20%.	No dose adjustment is recommended.
Clarithromycin	CT	Dabigatran exposure in healthy subjects was increased by about 15% in the presence of clarithromycin (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph).	No dose adjustment is recommended. Caution should be exercised.
Diclofenac	CT	When dabigatran etexilate was co-administered with diclofenac, pharmacokinetics of both drugs appeared unchanged.	No dose adjustment is recommended. Use with caution (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1.)
Digoxin	CT	When dabigatran etexilate was co-administered with digoxin, no PK-interaction was observed.	No dose adjustment is recommended.
Ketoconazole	CT	Dabigatran exposure was increased 150% after single and multiple doses of ketoconazole (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph).	**Co-administration with PRADAX is contraindicated.** (see CONTRAINDICATIONS).
Pantoprazole	CT	When dabigatran etexilate was co-administered with pantoprazole, a decrease in dabigatran AUC of about 30 % was observed. In the Phase III study, RELY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (-11%) (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph).	No dose adjustment is recommended. Diminished clinical effect may occur, as may be expected for any drug resulting in an increase in gastric pH during PRADAX administration.
Rifampicin	CT	After 7 days of treatment with 600 mg rifampicin qd total dabigatran AUC0-∞ and Cmax were reduced by 67% and 66% compared to the reference treatment, respectively (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph).	Concomitant use of PRADAX with rifampicin should, in general, be avoided. Concomitant use would be expected to result in substantially diminished anticoagulant effect of PRADAX.
Verapamil	CT	When dabigatran etexilate, given at 150 mg once daily, was co-administered with moderate doses of oral verapamil, the Cmax and AUC of dabigatran were increased, but the magnitude of this change varied depending on the timing of administration and the formulation of verapamil used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic Interactions* in the Product Monograph).	Dosing should be reduced to 150 mg PRADAX daily in patients treated for prevention of VTE after hip- or knee-replacement surgery who concomitantly receive dabigatran etexilate and verapamil. To minimize potential for interaction, PRADAX should be given at least two hours before verapamil. Caution should be exercised.
			Although no dose adjustment is recommended for AF patients, to minimize potential for interaction, PRADAX should be given at least two hours before verapamil. Caution should be exercised.
Quinidine	CT	Dabigatran exposure in healthy subjects was increased by 53 % in the presence of quinidine.	Adjust dosing for patients treated for prevention of VTE after hip- or knee-replacement surgery to 150 mg daily PRADAX. Caution should be exercised.
			Although no dose adjustment is recommended for AF patients, to minimize potential for interaction, PRADAX should be given at least two hours before quinidine, if possible. Caution should be exercised.

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

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 St. 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, TT, ECT) is adequate to reliably assess the anticoagulant activity of dabigatran following PRADAX administration. 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 (WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, in the Product Monograph).

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec at trough (when the next dose is due) is associated with a higher risk of bleeding.

Note that a PT (INR) test is not useful to assess the anticoagulant activity of PRADAX.

Drug-Lifestyle Interactions

No direct interaction between dabigatran etexilate and alcohol was demonstrated in animal models or has been hypothesized.

The effect of PRADAX on the ability to drive and use machines has not been investigated. However, no such interaction is to be expected.

Administration

DOSAGE AND ADMINISTRATION

PRADAX should be taken orally, with the entire capsule to be swallowed whole. The capsule should not be chewed, broken, or opened.

PRADAX should be taken regularly, as prescribed, to ensure optimal effectiveness. All temporary discontinuations should be avoided, unless medically indicated.

Recommended Dose and Dosage Adjustment

- *Prevention of stroke and systemic embolism in patients with atrial fibrillation:* The recommended dose of PRADAX is 300 mg daily, taken orally as one 150 mg capsule twice a day.

Elderly:

- *Prevention of stroke and systemic embolism in patients with atrial fibrillation:* Patients aged 80 years and above should be treated with a dose of 220 mg of PRADAX daily, taken orally as one 110 mg capsule twice a day (see WARNINGS AND PRECAUTIONS, Geriatrics, and CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Tables 24 and 25, in the Product Monograph).
- The usual recommended dose for most geriatric patients under the age of 80 years is 300 mg daily, taken orally as one 150 mg capsule twice a day (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Tables 24 and 25, in the Product Monograph). However, in geriatric patients, especially those over the age of 75 with at least one other risk factor for bleeding (see WARNINGS AND PRECAUTIONS, Bleeding, Table 2), the administration of a dose of 220 mg of PRADAX daily, taken orally as one 110 mg capsule twice a day, may be considered. It should be noted, however, that the effectiveness of stroke prevention may be expected to be lessened with this dosage regimen, compared to that of the usual one of 300 mg of PRADAX daily. As with any anticoagulant, caution is required when prescribing PRADAX to the elderly (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Bleeding).

Patients at risk of bleeding: *Prevention of stroke and systemic embolism in patients with atrial fibrillation:* Patients with an increased risk of bleeding (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1), should be closely monitored clinically (looking for signs of bleeding or anemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. As for any anticoagulant, PRADAX is NOT indicated in patients at excessive risk of bleeding (see CONTRAINDICATIONS).

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.

There are no data to support use in patients with severe renal impairment (CrCl <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 in the Product Monograph).

- *Patients with atrial fibrillation treated for prevention of stroke and systemic embolism having moderate renal impairment (CrCl 30-50 mL/min):* No dose adjustment is recommended (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, *Renal Impairment* in the Product Monograph). Patients with moderate renal impairment (CrCl 30-50 mL/min) should be treated with a daily dose

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of PRADAX at 300 mg taken orally as one 150 mg capsule twice daily, with caution. Regular assessment of renal status is required in these patients (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Renal). A coagulation test, such as aPTT (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

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

Creatinine clearance (mL/min) =

Males: $\frac{(140\text{-age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100mL)}}$

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

P-glycoprotein inhibitors: P-gp inhibitors like verapamil, quinidine, and amiodarone may be expected to increase systemic exposure to dabigatran. Combination use with oral ketoconazole is contraindicated (see CONTRAINDICATIONS).

- *Patients with atrial fibrillation treated for prevention of stroke and systemic embolism:* No dose adjustment is recommended in patients concomitantly receiving amiodarone, quinidine or verapamil (see DRUG INTERACTIONS, Table 4, Summary of Drug-Drug Interactions; and ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic interactions* in the Product Monograph). Patients should be treated with a daily dose of 300 mg PRADAX taken orally as one 150 mg capsule twice daily. To minimize potential for interaction, PRADAX should be given at least two hours before verapamil (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, *Pharmacokinetic interactions* in the Product Monograph). Caution should be exercised. Close clinical surveillance is recommended.

Drugs that increase gastric pH, such as antacids, protein pump inhibitors (PPI): Diminished clinical effect for antacids may occur (see DRUG INTERACTIONS, Table 4, Summary of Drug-Drug Interactions). Although no dosage adjustment is generally necessary, administer PRADAX at least two hours before antacids, if possible, to minimize interaction potential. No dose adjustment is required for pantoprazole or other PPIs.

Concomitant antithrombotic use: Concomitant use of ASA or clopidogrel with PRADAX in patients with atrial fibrillation approximately doubled the risk of major bleed, irrespective of dose of PRADAX used. A similar increase was noted with such concomitant use with the study comparator, warfarin. These observations contrasted with little apparent additional improvement in stroke and systemic embolic events with combined antithrombotic use and PRADAX (or warfarin).

Concomitant use of PRADAX with an antithrombotic is not recommended for prevention of cardiogenic thromboembolic stroke in patients with atrial fibrillation. Concomitant use of ASA or other antiplatelet agents based on medical need to prevent myocardial infarction should be undertaken with caution. Close clinical surveillance is recommended.

Acute myocardial infarction (AMI): Consideration should be given to discontinuing PRADAX in the setting of acute myocardial infarction should the treatment of myocardial infarction involve invasive procedures, such as percutaneous coronary revascularization, or coronary artery bypass surgery. Similar consideration should be given if thrombolytic therapy is to be initiated, because bleeding risk may increase. Patients with AMI should be treated according to current clinical guidelines for that disorder. In this setting, PRADAX may be resumed for the prevention of stroke and systemic embolism upon completion of these revascularization procedures.

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. No dose adjustment deemed necessary.

Switching from PRADAX treatment to parenteral anticoagulant:

- In patients with atrial fibrillation treated for prevention of stroke and systemic embolism: wait **12 hours** after the last dose of PRADAX before switching to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to PRADAX: If deemed medically appropriate, treatment with PRADAX should be initiated 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]).

Switching from Vitamin K antagonists to PRADAX: If deemed medically appropriate, PRADAX should only be started after Vitamin K antagonists have been discontinued, and the patient's INR is found to be below 2.0.

Cardioversion: Patients can be maintained on PRADAX while being cardioverted.

Missed Dose: *Prevention of stroke and systemic embolism in patients with atrial fibrillation:* If the prescribed dose of PRADAX is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. A forgotten PRADAX dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses. For optimal effect and safety, it is important to take PRADAX regularly twice a day, at approximately 12-hour intervals.

Administration

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

The capsule should be swallowed intact. It should not be opened, broken, or chewed (see ACTION AND CLINICAL PHARMACOLOGY in the full Product Monograph, Pharmacokinetics in the Product Monograph).

SUPPLEMENTAL PRODUCT INFORMATION

Adverse Reactions:

Liver Function Tests: In the long-term RELY study, observed abnormalities of liver function tests (LFT) are presented below in Table 5.

Table 5: Liver Function Tests in the RELY trial

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Total treated	5,983 (100.0)	6,059 (100.0)	5,999 (100.0)
ALT or AST >3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST >5xULN	36 (0.7)	45 (0.7)	50 (0.8)
ALT or AST >3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	21 (0.4)

OVERDOSAGE

There is no antidote to dabigatran etexilate or dabigatran. Doses of PRADAX beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of PRADAX. 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. Appropriate standard treatment, e.g., surgical hemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or the transfusion of fresh frozen plasma.

As protein binding is low, dabigatran can be dialysed, although there is limited clinical experience in using dialysis in this setting. Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been clearly demonstrated. 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 should be given according to the physician's judgement.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Product Monograph is available upon request or at www.boehringer-ingelheim.ca

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PrLYRICA® PREGABALIN

PRESCRIBING SUMMARY

PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION
Analgesic Agent

INDICATIONS AND CLINICAL USE
LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia and spinal cord injury. LYRICA is indicated for the management of pain associated with fibromyalgia. The efficacy of LYRICA in the management of pain associated with fibromyalgia for up to 6 months was demonstrated in a placebo-controlled trial in patients who had initially responded to LYRICA during a 6-week open-label phase.

Use in Special Populations
Geriatrics (>65 years of age): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see *WARNINGS AND PRECAUTIONS, Geriatrics* [*>65 years of age*]).

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established.

Renal: There have been reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregab alin showed reversibility of this event in some cases (see Product Monograph, *WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions; and DOSAGE AND ADMINISTRATION*). Because pregabalin is eliminated primarily by renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients or those with renal impairment (see Product Monograph, *ACTION AND CLINICAL PHARMACOLOGY* and *DOSAGE AND ADMINISTRATION*).

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labour and Delivery: The effects of pregabalin on labour and delivery in pregnant women are unknown.

Nursing Women: It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

CONTRAINDICATIONS
Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Angioedema: There have been post-marketing reports of angioedema in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), neck, throat, and larynx/upper airway. There have been reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Some of these patients did not have reported previous history/episode(s) of angioedema. LYRICA should be immediately discontinued in patients with these symptoms. During the pre-marketing assessment of pregabalin in clinical trials, angioedema was reported as a rare reaction (see Product Monograph, *ADVERSE REACTIONS,* Less Common Clinical Trial Adverse Reactions and Post-Marketing Adverse Drug Reactions). *Caution should be exercised when prescribing* LYRICA to patients with previous history/episode(s) of angioedema and related events. In addition, patients who are taking other drugs associated with angioedema (eg, ACE-inhibitors) may be at increased risk of developing this condition.

Hypersensitivity: There have been post-marketing reports of hypersensitivity reactions (e.g. skin redness, blisters, hives, rash, dyspnea, and wheezing). Pregabalin should be discontinued immediately if such symptoms occur (see Product Monograph, Post-Marketing Adverse Drug Reactions).

Renal Failure: In both clinical trials of various indications and post-marketing database, there are reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Caution is advised when prescribing pregabalin to the elderly or those with any degree of renal impairment (see Product Monograph, Special Populations, *Renal;* Abrupt or Rapid Discontinuation; *ADVERSE REACTIONS,* Post-Marketing Adverse Drug Reactions; and *DOSAGE AND ADMINISTRATION*).

Tumorigenic Potential: In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Ophthalmological Effects: In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see Product Monograph, *Post-Marketing Adverse Drug Reactions*).

Patients should be informed that if changes in vision occur, they should notify their physician.

Peripheral Edema: LYRICA may cause peripheral edema. In controlled peripheral neuropathic pain and fibromyalgia clinical trials, pregabalin treatment caused peripheral edema in 9% of patients compared with 3% of patients in the placebo group. In these studies, 0.7% of pregabalin patients and 0.3% of placebo patients withdrew due to peripheral edema (see Product Monograph, *ADVERSE REACTIONS, Peripheral Edema*).

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Congestive Heart Failure: In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate (between 0.1% and 1%; see Product Monograph, *ADVERSE REACTIONS,* Less Common Clinical Trial Adverse Reactions).

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see Product Monograph, *ADVERSE REACTIONS,* Post-marketing Adverse Drug Reactions). Although this adverse reaction has mostly been observed in elderly cardiovascular-compromised patients during pregabalin treatment for a neuropathic pain indication, some cases have occurred in patients without reported edema or previous history of cardiovascular disease. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Gastrointestinal: There have been post-marketing reports of events related to reduced lower gastrointestinal tract function (eg. intestinal obstruction, paralytic ileus, and constipation) in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with LYRICA, primarily in combination with other *medications that have the potential to produce constipation.* Some of these events were considered serious and required hospitalization. In a number of instances, patients were taking opioid analgesics including tramadol.

Caution should be exercised when LYRICA and opioid analgesics are used in combination, and measures to prevent constipation may be considered, especially in female patients and elderly as they may be at increased risk of experiencing lower gastrointestinal-related events (see Product Monograph, *ADVERSE REACTIONS,* Post-Marketing Adverse Drug Reactions).

Weight Gain: LYRICA may cause weight gain. In pregabalin-controlled peripheral neuropathic pain and fibromyalgia clinical trials with durations of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 3% of placebo-treated patients. Few patients treated with pregabalin (0.6%) withdrew from controlled trials due to weight gain (see Product Monograph, *ADVERSE REACTIONS,* Weight Gain).

Pregabalin-associated weight gain was related to dose and duration of exposure. Pregabalin-associated weight gain did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema and was not necessarily due to edema-related events (see Product Monograph, *WARNINGS AND PRECAUTIONS,* Peripheral Edema).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, *in controlled and longer-term open-label clinical trials* with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}).

Dizziness and Somnolence: LYRICA may cause dizziness and somnolence. In controlled studies, pregabalin caused dizziness in 32% of patients compared to 8% in placebo. Somnolence was experienced by 17% and 4% of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses. In these studies, dizziness and somnolence led to withdrawal of 5% (placebo: 0.5%) and 3% (placebo: 0.1%) of the pregabalin-treated patients, respectively. For the remaining patients who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 35% and 49% of the patients, respectively (see Product Monograph, *ADVERSE REACTIONS,* Tables 2, 4, and 11, and Post-Marketing Adverse Drug Reactions).

Abrupt or Rapid Discontinuation: Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see Product Monograph, *ADVERSE REACTIONS, Adverse Events Following Abrupt or Rapid Discontinuation*).

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

Clinical Trial Adverse Drug Reactions
Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Neuropathic Pain: The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema, and dry mouth. Adverse events were usually mild to moderate in intensity.

Adverse Events from a Controlled Clinical Study in Neuropathic Pain Associated with Spinal Cord Injury: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: somnolence, dizziness, asthenia, dry mouth, edema, myasthenia, constipation, thinking abnormal, amblyopia, and amnesia. Adverse events were usually mild to moderate in intensity.

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Most Common Adverse Events in Controlled Clinical Studies in Fibromyalgia: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness (37.5%), somnolence (18.6%), weight gain (10.6%), dry mouth (7.9%), blurred vision (6.7%), peripheral edema (6.1%), constipation (5.8%), and disturbance in attention (5.3%). Adverse events were usually mild to moderate in intensity.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect a patient has had a serious or unexpected reaction to this drug, you may notify Health Canada by telephone: 1-866-234-2345.

ADMINISTRATION

DOSING CONSIDERATIONS

Patients with Impaired Renal Function

Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In some elderly patients and those with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in Supplemental Product Information).

Adults

Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently (see Product Monograph, *ADVERSE REACTIONS*, Tables 1 and 5). Doses above 600 mg/day have not been studied and are not recommended.

Neuropathic pain associated with spinal cord injury: The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered. Doses above 600 mg/day have not been studied and are not recommended.

Pain associated with fibromyalgia: The recommended dosage is 300 to 450 mg/day, given in two divided doses. The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Based on individual response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg BID (450 mg/day). In some patients, efficacy of LYRICA has been demonstrated within the first week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials of fibromyalgia, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced significantly higher rates of adverse events and discontinued the trial more frequently (see Product Monograph, *ADVERSE REACTIONS*, Tables 7 and 10). In view of the dose-related adverse events, the decision to treat patients with doses above 450 mg/day should be based on clinical judgment of the treating physician. Doses above 600 mg/day have not been studied and are not recommended.

ADMINISTRATION

LYRICA is given orally with or without food.

STUDY REFERENCES

References:

1. LYRICA Product Monograph, Pfizer Canada Inc., June 21, 2010.
2. Moulin DE *et al.* Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage 2007*;12:13-21.
3. Arnold LM *et al.* A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain* 2008;9:792-805.

   14-week, randomized, double-blind, multiple-dose, placebo-controlled, multicentre study. 745 patients who had moderate-to-severe pain, i.e. mean baseline score (mean of the last 7 daily diary pain scores prior to study medication) of ≥4, and a diagnosis of fibromyalgia based on the ACR criteria. This study used an enriched population as placebo responders (≥30% reduction in mean pain scores) during the one-week run-in phase were discontinued and did not enter the double-blind phase. 1.6% of patients screened (n=19/1,195) were reported to be placebo responders. Patients were randomized to LYRICA 300 mg/day (n=183), 450 mg/day (n=190), 600 mg/day (n=188), or placebo (n=184). Patients were allowed to take acetaminophen up to 4 g/day as needed for pain relief. The number of completers was: LYRICA 300 mg/day (n=123), 450 mg/day (n=125), 600 mg/day (n=113), or placebo (n=125). The primary endpoint was the reduction in endpoint mean pain scores. Pain scores rated on 11-point numerical scale from 0 (no pain) to 10 (worst possible pain) during the past 24 hours. Mean baseline pain scores were 6.7 for LYRICA 300 mg/day, 6.7 for 450 mg/day, 6.8 for 600 mg/day, and 6.6 for placebo.
4. Crofford LJ *et al.* Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008;136:419-31.

   26-week, long-term relapse observation study. Patients who met the ACR criteria for fibromyalgia and who had a score of ≥40 on the pain Visual Analog Scale (VAS) were eligible to enter a 6-week, open-label, dose-optimization phase. During this phase, patients were titrated up to a total daily dose of 300 mg, 450 mg, or 600 mg. 566 LYRICA responders were randomized in the double-blind phase to either their optimized LYRICA dose (n=279) or to placebo (n=287). 38% of LYRICA responders completed 26 weeks of treatment vs 19% on placebo. The primary endpoint was time to loss of therapeutic response. Loss of therapeutic response was defined as having either a <30% reduction in pain VAS score, or worsening of symptoms necessitating alternate treatment. Responders were defined as having a ≥50% reduction in pain on the VAS and self-rating on the Patient Global Impression of Change scale of "much improved" or "very much improved".
5. Freynhagen R *et al.* Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005;115:254-63.

   In a 12-week, multicentre, randomized, double-blind, placebo-controlled study, 338 patients with either DPN (n=249) or PHN (n=89) were randomized to receive BID flexible-dose pregabalin (150-600 mg/day), fixed-dose pregabalin (600 mg/day) or placebo. In the flexible-dose arm, dose could be adjusted up or down over the first four weeks based on patients' individual response and tolerability. The primary efficacy measurement was mean pain score at endpoint, derived from ratings recorded by patients in a daily diary on an 11-point numerical pain rating scale (0=no pain, 10=worst possible pain). A significant difference in pain scores versus placebo was seen in the flexible dose range 150-600 mg/day ($p \leq 0.05$, weeks 2-3 and $p \leq 0.01$, weeks 4-12), and the fixed dose of 600 mg/day ($p \leq 0.05$, week 1 and $p \leq 0.01$, weeks 2-12).
6. Mease PJ *et al.* A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008;35:502-14.

   Multicentre, double-blind, 13-week, randomized trial. 748 patients who met the ACR criteria for fibromyalgia and who had an average mean pain score of ≥4 on an 11-point numeric rating scale (NRS) during the baseline assessment were randomized to LYRICA 300 mg/day (n=185), 450 mg/day (n=183), 600 mg/day (n=190), or placebo (n=190). Patients were allowed to take acetaminophen up to 4 g/day as needed for pain relief. The number of completers was: LYRICA 300 mg/day (n=123), 450 mg/day (n=121), 600 mg/day (n=111), or placebo (n=130). The primary endpoint was the reduction in endpoint mean pain scores (mean of the last 7 daily pain scores while on study medication). Pain-related sleep difficulties were assessed using the Medical Outcomes Study-Sleep Scale (MOS-SS), a scale that runs from 0-100. Mean baseline MOS-SS score for overall sleep problem index was 65.0.

SUPPLEMENTAL PRODUCT INFORMATION

Warnings and Precaution

See the Product Monograph for further information on the following: tumorigenic potential, ophthalmological effects, peripheral edema, congestive heart failure, weight gain, dizziness and somnolence, sexual function/reproduction, and special populations.

Drug Interactions

Overview: Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (≤2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Drug Abuse and Dependence/Liability: Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

ADMINISTRATION

Dosage Adjustment Based on Renal Function: Dosing adjustment should be based on creatinine clearance (CL_{cr}), as indicated in Table 1.

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table below).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a] Recommended Dose Escalation*				Dose Regimen
	Starting dose	up to		Maximum daily dose	
≥60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
<15	25	25-50	50-75	75	QD
Supplementary dosage following hemodialysis (mg)[b]					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50-75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

* Based on individual patient response and tolerability.

[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[b] Supplementary dose is a single additional dose.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans: The highest known dose of pregabalin received in the clinical development program in which there was no fatal outcome was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin. In post-marketing experience, fatal outcomes in cases in which pregabalin has been taken in combination with other medications have been reported with a pregabalin overdose as low as 800 mg in a day. In none of these cases has pregabalin been established as the cause of death or in pregabalin monotherapy. The lowest fatal dose with pregabalin alone has not yet been identified.

The most commonly reported adverse events observed when pregabalin was taken in overdose (dose range from 800 mg/day up to 11,500 mg as a single dose) included affective disorder, somnolence, confusional state, depression, agitation, and restlessness.

Treatment or Management of Overdose: There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Hemodialysis: Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

Availability of Dosage Forms

LYRICA is available in dosage strengths of 25 mg, 50 mg, 75 mg, *100 mg*, 150 mg, 200 mg*, 225 mg, and 300 mg capsules.*

* Not commercially available in Canada

For a copy of the Product Monograph or full Prescribing Information, please contact: Pfizer Canada Medical Information at 1-800-463-6001 or visit www.pfizer.ca.

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2011 Congress-at-a-Glance

wednesday june 15

07:00 - 08:45	Continental Breakfast
08:00 - 17:15	Neurosurgery Resident Review – Peripheral Nerve Surgery ***Rajiv Midha, Shobhan Vachhrajani & Ryojo Akagami***
09:00 - 17:15	Neurology Resident Review – Multiple Sclerosis ***Anthony Traboulsee***
09:00 - 17:15	ALS ***Charles Krieger***
09:00 - 12:15	Stroke ***Philip Teal***
09:00 - 12:15	Update on Frontotemporal Dementia ***Ging-Yuek Robin Hsiung***
12:30 - 13:45	Lunch & Poster Viewing
12:30 - 13:45	Co-developed Industry Symposium (Stroke)
12:30 - 13:45	Co-developed Industry Symposium (Headache)
14:00 - 17:15	Headache ***Gordon Mackie***
14:00 - 17:15	Neurocritical Care ***Draga Jichici & Jeanne Teitelbaum***
14:00 - 17:15	Functional Neurosurgery ***Christopher Honey***
17:15 – 19:30	Exhibitors Reception

thursday june 16

07:00 - 08:15	Continental Breakfast
08:30 - 09:15	Distinguished Guest Lecture
09:30 - 17:00	Child Neurology Day – Tibbles Lecture: ***Ingrid Scheffer***
09:30 - 12:30	CNS / CSCN Plenary & Chair's Select Abstracts - Gloor Lecture: ***Angela Vincent,*** Richardson Lecture: ***Judy Illes***
09:30 - 12:30	CNSS Plenary & Chair's Select Abstracts - Penfield Lecture: ***William Couldwell,*** CNSS Society Lecture: ***Allan Taylor***
12:45 - 14:00	Lunch, Exhibit & Poster Viewing
12:45 - 14:00	Co-developed Industry Symposium (Epilepsy)
12:45 - 14:00	Co-developed Industry Symposium (Neuropathic Pain)
14:15 - 17:30	Multiple Sclerosis ***Anthony Traboulsee***
14:15 - 17:30	Neurovascular & Interventional Neuroradiology ***Gary Redekop***
14:15 - 17:30	EEG ***Seyed Mirsattari***
14:15 - 17:30	Spine ***Eric Massicotte***
18:00 - 20:00	Movement Disorders SIG ***Silke Cresswell***
18:00 - 20:00	Headache SIG ***Gordon Robinson***
18:00 - 20:00	Neuromuscular Diseases SIG ***Kristine Chapman***
18:00 - 20:00	Epilepsy Video SIG ***Richard McLachlan***

friday june 17

07:00 - 08:15	Continental Breakfast
08:30 - 11:15	Platform Sessions
11:30 - 13:15	Grand Rounds
13:15 - 15:00	Lunch, Exhibit & Poster Author Stand-by Tours
13:15 - 15:00	Digital Poster and Exhibit Viewing
13:15 - 14:45	Scotiabank Private Client Group-Wills & Estate Planning
15:00 - 18:15	Epilepsy ***Nizam Ahmed***
15:00 - 18:15	Advances in Neuro-Oncology ***David Eisenstat***
15:00 - 18:15	Neuro-ophthalmology ***William Fletcher***
15:00 - 18:15	Advances in Neurobiology ***Zelma Kiss & Peter Smith***
15:00 - 18:15	Neuromuscular Diseases ***Mike Nicolle***
15:00 - 18:15	Evidence-Based Neurosurgery in Modern Day Practice ***Brian Toyota***
19:00 - 24:00	Presidents' Social Event - A Night at the Commodore

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The Neurological Sciences Foundation of Canada (NSFC) is a charitable organization. The NSFC's work is entirely dependent on donations and raises money annually in support of activities and initiatives of importance to neurologists, neurosurgeons and the neurological community.

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- the Canadian Association of Neuroscience Nurses
- the Canadian Association of Electroneurophysiology Technologists
- the Association of Electromyography Technologists of Canada
- the Canada Cuba Project, through the recently formed CNSF International Development Committee
- Think First
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