HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PRADAXA Capsules safely and effectively. See full prescribing information for PRADAXA Capsules.

PRADAXA® (dabigatran etexilate) capsules, for oral use
Initial U.S. Approval: 2010

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.6, 2.7, 2.8, 5.1).

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.3). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

---------- INDICATIONS AND USAGE----------
PRADAXA Capsules is a direct thrombin inhibitor indicated:
- To reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (1.1)
- For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in adult patients who have been treated with a parenteral anticoagulant for 5-10 days (1.2)
- To reduce the risk of recurrence of DVT and PE in adult patients who have been previously treated (1.3)
- For the prophylaxis of DVT and PE in adult patients who have undergone hip replacement surgery (1.4)
- For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days (1.5)
- To reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated (1.6)

----------DOSAGE AND ADMINISTRATION----------
- Non-valvular Atrial Fibrillation in Adult Patients:
  - For patients with CrCl > 30 mL/min: 150 mg orally, twice daily (2.2)
  - For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (2.2)
- Treatment of DVT and PE in Adult Patients:
  - For patients with CrCl > 30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation (2.2)
- Reduction in the Risk of Recurrence of DVT and PE in Adult Patients:
  - For patients with CrCl > 30 mL/min: 150 mg orally, twice daily after previous treatment (2.2)
- Prophylaxis of DVT and PE Following Hip Replacement Surgery in Adult Patients:
  - For patients with CrCl > 30 mL/min: 110 mg orally first day, then 220 mg once daily (2.2)
- Treatment of Pediatric VTE:
  - For pediatric patients: weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant (2.3)
- Reduction in the Risk of Recurrence of Pediatric VTE:
  - For pediatric patients: weight-based dosage, twice daily after previous treatment (2.3)
- Pradaxa Capsules are NOT substitutable on a milligram-to-milligram basis with other dabigatran etexilate dosage forms
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.6, 2.7)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.8)

---------- DOSAGE FORMS AND STRENGTHS ----------
Capsules: 75 mg, 110 mg and 150 mg (3)

---------- CONTRAINDICATIONS ----------
- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)
- Mechanical prosthetic heart valve (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Bleeding: PRADAXA can cause serious and fatal bleeding (5.2)
- Bioprosthetic heart valves: PRADAXA use not recommended (5.4)
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome: PRADAXA use not recommended (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (> 15%) are gastrointestinal adverse reactions and bleeding (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS----------
- P-gp inducers: Avoid coadministration with PRADAXA (5.5)
- P-gp inhibitors in adult patients with CrCl 30-50 mL/min: Reduce dosage or avoid (7)
- P-gp inhibitors in adult patients with CrCl < 30 mL/min: Not recommended (7)

---------- USE IN SPECIFIC POPULATIONS ----------
- Lactation: Breastfeeding not recommended (8.2)
- Geriatric Use: Risk of bleeding increases with age (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.6, 2.7, 2.8) and Warnings and Precautions (5.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of PRADAXA and neuraxial procedures is not known**

***[see Warnings and Precautions (5.3)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation in Adult Patients

PRADAXA Capsules is indicated to reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.

1.2 Treatment of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients

PRADAXA Capsules is indicated for the treatment of deep venous thrombosis and pulmonary embolism in adult patients who have been treated with a parenteral anticoagulant for 5-10 days.

1.3 Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients

PRADAXA Capsules is indicated to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in adult patients who have been previously treated.

1.4 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Adult Patients Following Hip Replacement Surgery

PRADAXA Capsules is indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism in adult patients who have undergone hip replacement surgery.

1.5 Treatment of Venous Thromboembolic Events in Pediatric Patients

PRADAXA Capsules is indicated for the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days *[see Dosage and Administration (2.3)]*.

1.6 Reduction in the Risk of Recurrence of Venous Thromboembolic Events in Pediatric Patients

PRADAXA Capsules is indicated to reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated *[see Dosage and Administration (2.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

Dabigatran etexilate is available in different dosage forms and not all dosage forms are approved for the same indications and age groups. In addition, there are differences between the dosage forms with respect to dosing due to differences in bioavailability. Do not substitute different dosage forms on a milligram-to-milligram basis and do not combine more than one dosage form to achieve the total dose *[see Clinical Pharmacology (12.3)]*.

2.2 Recommended PRADAXA Capsules Dosage for Adults

Indication	Dosage	
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF	CrCl > 30 mL/min:	150 mg twice daily
	CrCl 15 to 30 mL/min:	75 mg twice daily
	CrCl < 15 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:	Reduce dosage to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole.
	CrCl < 30 mL/min with concomitant use of P-gp inhibitors:	Avoid coadministration

Treatment of DVT and PE **Reduction in the Risk of Recurrence of DVT and PE**	CrCl > 30 mL/min:	150 mg twice daily
	CrCl ≤ 30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl < 50 mL/min with concomitant use of P-gp inhibitors:	Avoid coadministration
Prophylaxis of DVT and PE Following Hip Replacement Surgery	CrCl > 30 mL/min:	110 mg for first day, then 220 mg once daily
	CrCl ≤ 30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl < 50 mL/min with concomitant use of P-gp inhibitors:	Avoid coadministration

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation in Adult Patients
For patients with creatinine clearance (CrCl) > 30 mL/min, the recommended dosage of PRADAXA Capsules is 150 mg taken orally, twice daily. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dosage of PRADAXA Capsules is 75 mg twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with a CrCl < 15 mL/min or on dialysis cannot be provided.

Treatment of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients
For patients with CrCl > 30 mL/min, the recommended dosage of PRADAXA Capsules is 150 mg taken orally, twice daily, after 5-10 days of parenteral anticoagulation. Dosing recommendations for patients with a CrCl ≤ 30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients
For patients with CrCl > 30 mL/min, the recommended dosage of PRADAXA Capsules is 150 mg taken orally, twice daily after previous treatment. Dosing recommendations for patients with a CrCl ≤ 30 mL/min or on dialysis cannot be provided *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Adult Patients Following Hip Replacement Surgery
For patients with CrCl > 30 mL/min, the recommended dosage of PRADAXA Capsules is 110 mg taken orally 1-4 hours after surgery and after hemostasis has been achieved, then 220 mg taken once daily for 28-35 days. If PRADAXA is not started on the day of surgery, after hemostasis has been achieved initiate treatment with 220 mg once daily. Dosing recommendations for patients with a CrCl ≤ 30 mL/min or on dialysis cannot be provided *[see Dosage and Administration (2.4), Use in Specific Populations (8.6), and Clinical Pharmacology (12.2, 12.3)]*.

2.3 Recommended PRADAXA Capsules Dosage for Pediatrics
PRADAXA Capsules can be used in pediatric patients aged 8 to less than 18 years of age who are able to swallow the capsules whole. Other age-appropriate pediatric dosage forms of dabigatran etexilate are available for pediatric patients less than 8 years of age. For the treatment of VTE in pediatric patients, initiate treatment following treatment with a parenteral anticoagulant for at least 5 days. For reduction in risk of recurrence of VTE, initiate treatment following previous treatment.

PRADAXA Capsules is dosed orally twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dosage of PRADAXA Capsules for the treatment of or reducing the risk of VTE in pediatric patients 8 to less than 18 years of age is based on the patient's actual weight as shown in Table 1 below. Administer PRADAXA twice daily. Adjust the dosage according to actual weight as treatment progresses *[see Dosage and Administration (2.5)]*.

Table 1 Weight-Based PRADAXA Capsules Dosage for Pediatric Patients Aged 8 to Less Than 18 Years

Actual Weight (kg)	Dosage (mg)	Number of Capsules Needed
11 kg to less than 16 kg	75 mg twice daily	one 75 mg capsule twice daily
16 kg to less than 26 kg	110 mg twice daily	one 110 mg capsule twice daily
26 kg to less than 41 kg	150 mg twice daily	one 150 mg capsule twice daily or two 75 mg capsules twice daily
41 kg to less than 61 kg	185 mg twice daily	one 110 mg capsule plus one 75 mg capsule twice daily
61 kg to less than 81 kg	220 mg twice daily	two 110 mg capsule twice daily
81 kg or greater	260 mg twice daily	one 150 mg capsule plus one 110 mg capsule twice daily or one 110 mg capsule plus two 75 mg capsules twice daily

2.4 Dosage Adjustments
Adult patients with renal impairment

Assess renal function prior to initiation of treatment with PRADAXA Capsules. Periodically assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly. Discontinue PRADAXA in patients who develop acute renal failure while on PRADAXA and consider alternative anticoagulant therapy.

Generally, in adult patients, the extent of anticoagulation does not need to be assessed. When necessary, use aPTT or ECT, and not INR, to assess for anticoagulant activity in adult patients on PRADAXA Capsules *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Reduce the dosage of PRADAXA Capsules to 75 mg twice daily *[see Warnings and Precautions (5.5), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Dosing recommendations for patients with CrCl ≤ 30 mL/min cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl < 50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Dosing recommendations for patients with CrCl ≤ 30 mL/min or on dialysis cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl < 50 mL/min *[see Dosage and Administration (2.5), Warnings and Precautions (5.5), Drug Interactions (7.3), and Clinical Pharmacology (12.2, 12.3)]*.

Pediatric patients with renal impairment
Treatment and reduction in risk of recurrence of VTE in pediatric patients
Due to lack of data in pediatric patients with eGFR < 50 mL/min/1.73 m^2 and the risk of increased exposure, avoid use of PRADAXA Capsules in these patients. Prior to the initiation of treatment with PRADAXA Capsules, estimate the glomerular filtration rate (eGFR) using the Schwartz formula: eGFR (Schwartz) = (0.413 x height in cm) / serum creatinine in mg/dL.

Treat patients with an eGFR > 50 mL/min/1.73 m^2 with the dosage according to Table 1 *[see Dosage and Administration (2.3)]*.

2.5 Administration
PRADAXA Capsules should be swallowed whole. PRADAXA Capsules should be taken with a full glass of water. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure *[see Clinical Pharmacology (12.3)]*.

If a dose of PRADAXA Capsules is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA Capsules should not be doubled to make up for a missed dose.

Consider administration with food if gastrointestinal distress occurs with PRADAXA Capsules.

2.6 Converting from or to Warfarin
When converting patients from warfarin therapy to PRADAXA Capsules, discontinue warfarin and start PRADAXA Capsules when the INR is below 2.0.

When converting from PRADAXA Capsules to warfarin, adjust the starting time of warfarin as follows:
Adults
- For CrCl ≥ 50 mL/min, start warfarin 3 days before discontinuing PRADAXA Capsules.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing PRADAXA Capsules.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA Capsules.
- For CrCl < 15 mL/min, no recommendations can be made.

Pediatrics
- For eGFR ≥ 50 mL/min/1.73 m^2, start warfarin 3 days before discontinuing PRADAXA Capsules.
- Pediatric patients with an eGFR < 50 mL/min/1.73 m^2 have not been studied. Avoid use of PRADAXA Capsules in these patients.

Because PRADAXA Capsules can increase INR, the INR will better reflect warfarin's effect only after PRADAXA Capsules has been stopped for at least 2 days *[see Clinical Pharmacology (12.2)]*.

2.7 Converting from or to Parenteral Anticoagulants
For adult and pediatric patients currently receiving a parenteral anticoagulant, start PRADAXA Capsules 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For adult patients currently taking PRADAXA Capsules wait 12 hours (CrCl ≥ 30 mL/min) or 24 hours (CrCl < 30 mL/min) after the last dose of PRADAXA Capsules before initiating treatment with a parenteral anticoagulant *[see Clinical Pharmacology (12.3)]*.

For pediatric patients currently taking PRADAXA, wait 12 hours after the last dose before switching to a parenteral anticoagulant.

2.8 Discontinuation for Surgery and Other Interventions
If possible, discontinue PRADAXA Capsules in adults 1 to 2 days (CrCl ≥ 50 mL/min) or 3 to 5 days (CrCl < 50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

For pediatric patients, discontinue PRADAXA Capsules 24 hours before an elective surgery (eGFR > 80 mL/min/1.73 m^2) or 2 days before an elective surgery (eGFR 50-80 mL/min/1.73 m^2). Pediatric patients with an eGFR <50 mL/min/1.73 m^2 have not been studied, avoid use of PRADAXA Capsules in these patients.

If surgery cannot be delayed, there is an increased risk of bleeding *[see Warnings and Precautions (5.2)]*. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.1, 5.3)]*. Use a specific reversal agent (idarucizumab) in case of emergency surgery or urgent procedures when

reversal of the anticoagulant effect of dabigatran is needed in adults. Efficacy and safety of idarucizumab have not been established in pediatric patients *[see Warnings and Precautions (5.2)]*. Refer to the idarucizumab prescribing information for additional information. Restart PRADAXA Capsules as soon as medically appropriate.

3 DOSAGE FORMS AND STRENGTHS

150 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a white opaque body imprinted in black with "R150".

110 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted in black with "R110".

75 mg capsules with a white opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a white opaque body imprinted in black with "R75".

4 CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- History of a serious hypersensitivity reaction to dabigatran, dabigatran etexilate, or to one of the excipients of the product (e.g., anaphylactic reaction or anaphylactic shock) *[see Adverse Reactions (6.1)]*
- Mechanical prosthetic heart valve *[see Warnings and Precautions (5.4)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA Capsules is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant and restart PRADAXA Capsules as soon as medically appropriate *[see Dosage and Administration (2.6, 2.7, 2.8)]*.

5.2 Risk of Bleeding

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA Capsules in patients with active pathological bleeding *[see Dosage and Administration (2.4)]*.

Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment *[see Clinical Pharmacology (12.2)]*.

Reversal of Anticoagulant Effect

In adults, a specific reversal agent (idarucizumab) for PRADAXA is available when reversal of the anticoagulant effect of dabigatran is needed:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

In pediatric patients, the efficacy and safety of idarucizumab have not been established.

Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited *[see Overdosage (10)]*. Prothrombin complex concentrates, or recombinant Factor VIIa may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of PRADAXA and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves

The safety and efficacy of PRADAXA Capsules in adult patients with bileaflet mechanical prosthetic heart valves was evaluated in the RE-ALIGN trial, in which patients with bileaflet mechanical prosthetic heart valves (recently implanted or implanted more than three months prior to enrollment) were randomized to dose-adjusted warfarin or 150 mg, 220 mg, or 300 mg of PRADAXA Capsules twice a day. RE-ALIGN was terminated early due to the occurrence of significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding (predominantly post-operative pericardial effusions requiring intervention for hemodynamic compromise) in the PRADAXA Capsules treatment arm as compared to the warfarin treatment arm. These bleeding and thromboembolic events were seen both in patients who were initiated on PRADAXA Capsules postoperatively within three days of mechanical bileaflet valve implantation, as well as in patients whose valves had been implanted more than three months prior to enrollment. Therefore, the use of PRADAXA is contraindicated in all patients with mechanical prosthetic valves *[see Contraindications (4)]*.

The use of PRADAXA for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended.

5.5 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation in Adult Patients
Reduce the dosage of PRADAXA Capsules to 75 mg twice daily when dronedarone or systemic ketoconazole is co-administered with PRADAXA Capsules in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of PRADAXA Capsules and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Drug Interactions (7.1) and Use in Specific Populations (8.6)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients
Avoid use of PRADAXA Capsules and concomitant P-gp inhibitors in patients with CrCl < 50 mL/min *[see Drug Interactions (7.2) and Use in Specific Populations (8.6)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Adult Patients Following Hip Replacement Surgery
Avoid use of PRADAXA Capsules and concomitant P-gp inhibitors in patients with CrCl < 50 mL/min *[see Drug Interactions (7.3) and Use in Specific Populations (8.6)]*.

Treatment and reduction in risk of recurrence of VTE in pediatric patients
The concomitant use of PRADAXA Capsules with P-gp-inhibitors has not been studied in pediatric patients but may increase exposure to dabigatran.

5.6 Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome
Direct-acting oral anticoagulants (DOACs), including PRADAXA, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple-positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Thrombotic Events after Premature Discontinuation *[see Warnings and Precautions (5.1)]*
- Risk of Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions (5.3)]*
- Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves *[see Warnings and Precautions (5.4)]*
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome *[see Warnings and Precautions (5.6)]*

The most serious adverse reactions reported with PRADAXA were related to bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Trials
Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study provided safety information on the use of two doses of PRADAXA Capsules and warfarin *[see Clinical Studies (14.1)]*. The numbers of patients and their exposures are described in Table 2. Limited information is presented on the 110 mg dosing arm because this dose is not approved.

Table 2 Summary of Treatment Exposure in RE-LY

	PRADAXA Capsules 110 mg twice daily	**PRADAXA Capsules 150 mg twice daily**	**Warfarin**
Total number treated	5,983	6,059	5,998
Exposure			
> 12 months	4,936	4,939	5,193
> 24 months	2,387	2,405	2,470
Mean exposure (months)	20.5	20.3	21.3
Total patient-years	10,242	10,261	10,659

Drug Discontinuation in RE-LY
The rates of adverse reactions leading to treatment discontinuation were 21% for PRADAXA Capsules 150 mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of PRADAXA Capsules were bleeding and gastrointestinal events (i.e., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Bleeding [see Warnings and Precautions (5.2)]
Table 3 shows the number of adjudicated major bleeding events during the treatment period in the RE-LY study, with the bleeding rate per 100 subject-years (%). Major bleeding is defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥ 2 g/dL, a transfusion of ≥ 2 units of packed red blood cells, bleeding at a critical site or with a fatal outcome. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 3 Adjudicated Major Bleeding Events in Treated Patients[a]

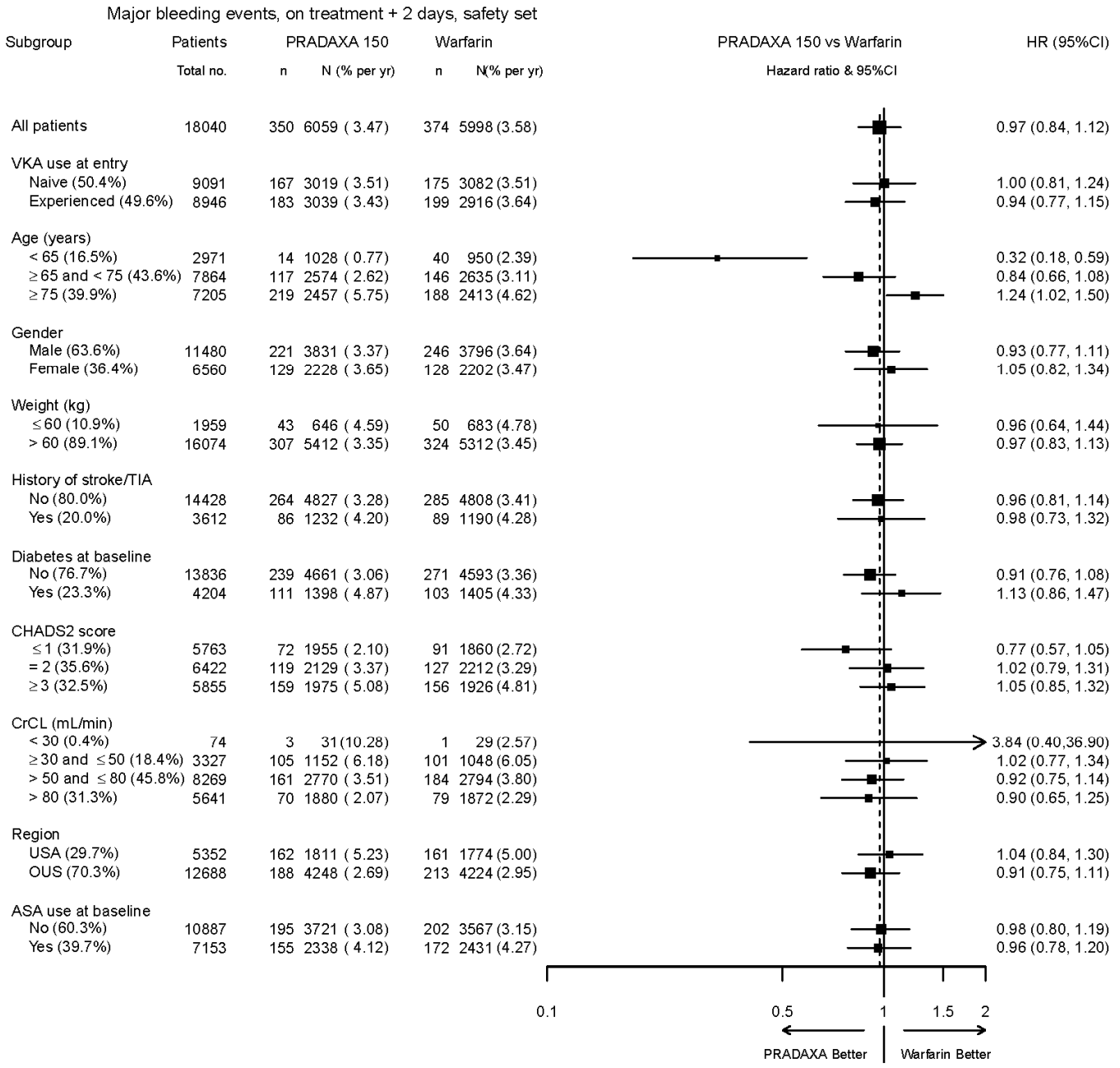
Event	PRADAXA Capsules 150 mg N = 6,059 n (%/year[b])	Warfarin N = 5,998 n (%/year[b])	PRADAXA Capsules 150 mg vs Warfarin HR (95% CI)
Major Bleeding[c]	350 (3.47)	374 (3.58)	0.97 (0.84, 1.12)
Intracranial Hemorrhage (ICH)[d]	23 (0.22)	82 (0.77)	0.29 (0.18, 0.46)
Hemorrhagic Stroke[e]	6 (0.06)	40 (0.37)	0.16 (0.07, 0.37)
Other ICH	17 (0.17)	46 (0.43)	0.38 (0.22, 0.67)
Gastrointestinal	162 (1.59)	111 (1.05)	1.51 (1.19, 1.92)
Fatal Bleeding[f]	7 (0.07)	16 (0.15)	0.45 (0.19, 1.10)
ICH	3 (0.03)	9 (0.08)	0.35 (0.09, 1.28)
Non-intracranial[g]	4 (0.04)	7 (0.07)	0.59 (0.17, 2.02)

[a]Patients during treatment or within 2 days of stopping study treatment. Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.
[b]Annual event rate per 100 pt-years = 100 * number of subjects with event/subject-years. Subject-years is defined as cumulative number of days from first drug intake to event date, date of last drug intake + 2, death date (whatever occurred first) across all treated subjects divided by 365.25. In case of recurrent events of the same category, the first event was considered.
[c]Defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥ 2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site or with fatal outcome.
[d]Intracranial bleed included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.
[e]On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14 Clinical Studies.
[f]Fatal bleed: Adjudicated major bleed as defined above with investigator reported fatal outcome and adjudicated death with primary cause from bleeding.
[g]Non-intracranial fatal bleed: Adjudicated major bleed as defined above and adjudicated death with primary cause from bleeding but without symptomatic intracranial bleed based on investigator's clinical assessment.

There was a higher rate of any gastrointestinal bleeds in patients receiving PRADAXA Capsules 150 mg than in patients receiving warfarin (6.6% vs 4.2%, respectively).

The risk of major bleeds was similar with PRADAXA Capsules 150 mg and warfarin across major subgroups defined by baseline characteristics (see Figure 1), with the exception of age, where there was a trend toward a higher incidence of major bleeding on PRADAXA Capsules (hazard ratio 1.2, 95% CI: 1.0 to 1.5) for patients ≥ 75 years of age.

Figure 1 Adjudicated Major Bleeding by Baseline Characteristics Including Hemorrhagic Stroke Treated Patients



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Gastrointestinal Adverse Reactions

Patients on PRADAXA Capsules 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in < 0.1% of patients receiving PRADAXA Capsules.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism

PRADAXA Capsules was studied in 4,387 patients in 4 pivotal, parallel, randomized, double-blind trials. Three of these trials were active-controlled (warfarin) (RE-COVER, RE-COVER II, and RE-MEDY), and one study (RE-SONATE) was placebo-controlled. The demographic characteristics were similar among the 4 pivotal

studies and between the treatment groups within these studies. Approximately 60% of the treated patients were male, with a mean age of 55.1 years. The majority of the patients were white (87.7%), 10.3% were Asian, and 1.9% were black with a mean CrCl of 105.6 mL/min.

Bleeding events for the 4 pivotal studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L or more, or leading to transfusion of 2 or more units of whole blood or red cells).

RE-COVER and RE-COVER II studies compared PRADAXA Capsules 150 mg twice daily and warfarin for the treatment of deep vein thrombosis and pulmonary embolism. Patients received 5-10 days of an approved parenteral anticoagulant therapy followed by 6 months, with mean exposure of 164 days, of oral only treatment; warfarin was overlapped with parenteral therapy. Table 4 shows the number of patients experiencing bleeding events in the pooled analysis of RE-COVER and RE-COVER II studies during the full treatment including parenteral and oral only treatment periods after randomization.

Table 4 Bleeding Events in RE-COVER and RE-COVER II Treated Patients

	Bleeding Events—Full Treatment Period Including Parenteral Treatment		
	PRADAXA Capsules 150 mg twice daily N (%)	**Warfarin N (%)**	**Hazard Ratio (95% CI)[c]**
Patients	**N=2,553**	**N=2,554**	
Major bleeding event[a]	37 (1.4)	51 (2.0)	0.73 (0.48, 1.11)
Fatal bleeding	1 (0.04)	2 (0.1)	
Bleeding in a critical area or organ	7 (0.3)	15 (0.6)	
Fall in hemoglobin ≥ 2 g/dL or transfusion ≥ 2 units of whole blood or packed red blood cells	32 (1.3)	38 (1.5)	
Bleeding sites for MBE[b]			
Intracranial	2 (0.1)	5 (0.2)	
Retroperitoneal	2 (0.1)	1 (0.04)	
Intraarticular	2 (0.1)	4 (0.2)	
Intramuscular	2 (0.1)	6 (0.2)	
Gastrointestinal	15 (0.6)	14 (0.5)	
Urogenital	7 (0.3)	14 (0.5)	
Other	8 (0.3)	8 (0.3)	
Clinically relevant non-major bleeding	101 (4.0)	170 (6.7)	0.58 (0.46, 0.75)
Any bleeding	411 (16.1)	567 (22.7)	0.70 (0.61, 0.79)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

The rate of any gastrointestinal bleeds in patients receiving PRADAXA Capsules 150 mg in the full treatment period was 3.1% (2.4% on warfarin).

The RE-MEDY and RE-SONATE studies provided safety information on the use of PRADAXA Capsules for the reduction in the risk of recurrence of deep vein thrombosis and pulmonary embolism.

RE-MEDY was an active-controlled study (warfarin) in which 1,430 patients received PRADAXA Capsules 150 mg twice daily following 3 to 12 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-MEDY study had a combined treatment duration of up to more than 3 years, with mean exposure of 473 days. Table 5 shows the number of patients experiencing bleeding events in the study.

Table 5 Bleeding Events in RE-MEDY Treated Patients

	PRADAXA Capsules 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI)[c]
Patients	**N=1,430**	**N=1,426**	
Major bleeding event[a]	13 (0.9)	25 (1.8)	0.54 (0.25, 1.16)
Fatal bleeding	0	1 (0.1)	
Bleeding in a critical area or organ	7 (0.5)	11 (0.8)	
Fall in hemoglobin ≥ 2 g/dL or transfusion ≥ 2 units of whole blood or packed red blood cells	7 (0.5)	16 (1.1)	
Bleeding sites for MBE[b]			
Intracranial	2 (0.1)	4 (0.3)	
Intraocular	4 (0.3)	2 (0.1)	
Retroperitoneal	0	1 (0.1)	
Intraarticular	0	2 (0.1)	
Intramuscular	0	4 (0.3)	
Gastrointestinal	4 (0.3)	8 (0.6)	
Urogenital	1 (0.1)	1 (0.1)	
Other	2 (0.1)	4 (0.3)	
Clinically relevant non-major bleeding	71 (5.0)	125 (8.8)	0.56 (0.42, 0.75)
Any bleeding	278 (19.4)	373 (26.2)	0.71 (0.61, 0.83)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

In the RE-MEDY study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA Capsules 150 mg was 3.1% (2.2% on warfarin).

RE-SONATE was a placebo-controlled study in which 684 patients received PRADAXA Capsules 150 mg twice daily following 6 to 18 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-SONATE study had combined treatment duration up to 9 months, with mean exposure of 165 days. Table 6 shows the number of patients experiencing bleeding events in the study.

Table 6 Bleeding Events in RE-SONATE Treated Patients

	PRADAXA Capsules 150 mg twice daily N (%)	Placebo N (%)	Hazard Ratio (95% CI)[c]
Patients	**N=684**	**N=659**	
Major bleeding event[a]	2 (0.3)	0	
Bleeding in a critical area or organ	0	0	
Gastrointestinal[b]	2 (0.3)	0	
Clinically relevant non-major bleeding	34 (5.0)	13 (2.0)	2.54 (1.34, 4.82)
Any bleeding	72 (10.5)	40 (6.1)	1.77 (1.20, 2.61)

Note: MBE can belong to more than one criterion.
[a]Patients with at least one MBE.
[b]Bleeding site based on investigator assessment. Patients can have more than one site of bleeding.
[c]Confidence interval

In the RE-SONATE study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA Capsules 150 mg was 0.7% (0.3% on placebo).

Clinical Myocardial Infarction Events
In the active-controlled VTE studies, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA Capsules [20 (0.66 per 100 patient-years)] than in those who received warfarin [5 (0.17 per 100 patient-years)]. In the placebo-controlled study, a similar rate of nonfatal and fatal clinical

myocardial infarction was reported in patients who received PRADAXA Capsules [1 (0.32 per 100 patient-years)] and in those who received placebo [1 (0.34 per 100 patient-years)].

Gastrointestinal Adverse Reactions
In the four pivotal studies, patients on PRADAXA Capsules 150 mg had a similar incidence of gastrointestinal adverse reactions (24.7% vs 22.7% on warfarin). Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA Capsules 7.5% vs 5.5% on warfarin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 3.0% vs 1.7%, respectively.

Hypersensitivity Reactions
In the 4 pivotal studies, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in 0.1% of patients receiving PRADAXA Capsules.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
PRADAXA Capsules was studied in 5,476 patients, randomized and treated in two double-blind, active-controlled non-inferiority trials (RE-NOVATE and RE-NOVATE II). The demographic characteristics were similar across the two studies and between the treatment groups within these studies. Approximately 45.3% of the treated patients were male, with a mean age of 63.2 years. The majority of the patients were white (96.1%), 3.6% were Asian, and 0.3% were black with a mean CrCl of 92 mL/min.

Bleeding events for the RE-NOVATE and RE-NOVATE II studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or retroperitoneal bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells, requiring treatment cessation or leading to re-operation.

The RE-NOVATE study compared PRADAXA Capsules 75 mg taken orally 1-4 hours after surgery followed by 150 mg once daily, PRADAXA Capsules 110 mg taken orally 1-4 hours after surgery followed by 220 mg once daily and subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who had undergone hip replacement surgery. The RE-NOVATE II study compared PRADAXA Capsules 110 mg taken orally 1-4 hours after surgery followed by 220 mg once daily and subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who had undergone hip replacement surgery. In the RE-NOVATE and RE-NOVATE II studies, patients received 28-35 days of PRADAXA Capsules or enoxaparin with median exposure of 33 days. Tables 7 and 8 show the number of patients experiencing bleeding events in the analysis of RE-NOVATE and RE-NOVATE II.

Table 7 Bleeding Events in RE-NOVATE Treated Patients

	PRADAXA Capsules 220 mg N (%)	**Enoxaparin N (%)**
Patients	**N=1,146**	**N=1,154**
Major bleeding event	23 (2.0)	18 (1.6)
Clinically relevant non-major bleeding	48 (4.2)	40 (3.5)
Any bleeding	141 (12.3)	132 (11.4)

Table 8 Bleeding Events in RE-NOVATE II Treated Patients

	PRADAXA Capsules 220 mg N (%)	**Enoxaparin N (%)**
Patients	**N=1,010**	**N=1,003**
Major bleeding event	14 (1.4)	9 (0.9)
Clinically relevant non-major bleeding	26 (2.6)	20 (2.0)
Any bleeding	98 (9.7)	83 (8.3)

In the two studies, the rate of major gastrointestinal bleeds in patients receiving PRADAXA Capsules and enoxaparin was the same (0.1%) and for any gastrointestinal bleeds was 1.4% for PRADAXA Capsules 220 mg and 0.9% for enoxaparin.

Gastrointestinal Adverse Reactions
In the two studies, the incidence of gastrointestinal adverse reactions for patients on PRADAXA Capsules 220 mg and enoxaparin was 39.5% and 39.5%, respectively. Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA Capsules 220 mg in 4.1% vs. 3.8% on enoxaparin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 0.6% vs 1.0%, respectively.

Hypersensitivity Reactions
In the two studies, drug hypersensitivity (such as urticaria, rash, and pruritus) was reported in 0.3% of patients receiving PRADAXA Capsules 220 mg.

Clinical Myocardial Infarction Events
In the two studies, clinical myocardial infarction was reported in 2 (0.1%) of patients who received PRADAXA Capsules 220 mg and 6 (0.3%) of patients who received enoxaparin.

Pediatric Trials

Treatment of VTE in Pediatric Patients
The safety of PRADAXA in the treatment of VTE in pediatric patients was studied in one phase III trial (DIVERSITY). The DIVERSITY study was a randomized, open-label, active-controlled, parallel-group trial comparing PRADAXA with standard of care – SOC (vitamin K antagonists, low molecular weight heparin, or

fondaparinux). There were 266 pediatric patients who received study treatment, 176 patients treated with PRADAXA and 90 patients treated with SOC. Patients on PRADAXA received age- and weight-adjusted dosages of an age-appropriate formulation of PRADAXA (capsules, pellets, or oral solution) twice daily.

Patients had a median age of 14 years (range: 0-17 years), 92% were white, and half the patients were male (50%). Following at least 5 days of parenteral anticoagulant therapy, the median duration of treatment with PRADAXA was 85 days (range: 1-105). Patients with estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73m^2 were excluded from the trial.

Bleeding
Data on adjudicated major bleeding, clinically relevant non-major (CRNM) bleeding and minor bleeding events, for the PRADAXA group and the SOC group in the DIVERSITY study, are reported in Table 9. There was no statistically significant difference in the time to first major bleeding event.

Table 9 Summary of All Adjudicated Bleeding Events During On-Treatment Period in DIVERSITY

	PRADAXA N (%)	**Standard of Care (SOC) N (%)**
Patients	**N=176**	**N=90**
Major bleeding event[1]	4 (2.3)	2 (2.2)
Fatal bleeding	0	1 (1.1)
Clinically relevant non-major bleeding	2 (1.1)	1 (1.1)
Minor bleeding	33 (19)	21 (23)
Major and clinically relevant non-major bleeding	6 (3.4)	3 (3.3)
Any bleeding	38 (22)	22 (24)

[1] Major bleeding event if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

Site-specific bleeding rates were comparable between the two arms, with the exception of the rate of any gastrointestinal bleeds (5.7% in PRADAXA arm vs 1.8% in SOC arm).

Gastrointestinal Adverse Reactions
The incidence of gastrointestinal adverse reactions for patients on PRADAXA and SOC was 32% and 12%, respectively, with the following occurring in ≥ 5% of patients taking PRADAXA: dyspepsia (including term gastro-esophageal reflux disease, gastric pH decreased and esophagitis) in 9% (vs 2%), upper abdominal pain in 5% (vs 1%), vomiting in 8% (vs 2%), nausea 5% (vs 4%), and diarrhea 5% (vs 1%).

Reduction in Risk of Recurrence of VTE in Pediatric Patients
The safety of PRADAXA in the reduction in the risk of recurrence of VTE in pediatric patients was studied in one open-label single-arm trial (Study 2). Study 2 enrolled patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study and received PRADAXA until the clinical risk factor resolved, or up to a maximum of 12 months. There were 213 pediatric patients treated with PRADAXA, in a similar fashion as in the DIVERSITY trial.

Patients had a median age of 14 years (range: 0-18 years), 91% were white, and 55% of patients were male. Patients previously enrolled on DIVERSITY accounted for 43% of patients enrolled on Study 2 (29% from PRADAXA arm and 14% from SOC arm). The median duration of treatment with PRADAXA in Study 2 was 42 weeks (range: 0-56 weeks), with 45% of patients completing the 12-month planned duration, 17% stopping due to resolution of VTE risk factors, 12% stopping due to failure to attain target dabigatran concentration and 6% had an adverse event leading to discontinuation.

During the on-treatment period of Study 2, 3 patients (1.4%) had a major bleeding event, 3 patients (1.4%) had a clinically relevant non-major bleeding event, and 44 patients (20%) had a minor bleeding event. The most common drug-related adverse reactions were dyspepsia (5%), epistaxis (3.3%), nausea (3.3%) and menorrhagia (2.8%).

The adverse reaction profile in pediatric patients was generally consistent with that of adult patients.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Agranulocytosis, neutropenia, thrombocytopenia
Gastrointestinal Disorders: Esophageal ulcer
Immune System Disorders: Angioedema
Renal and Urinary Disorders: Anticoagulant-related nephropathy
Skin and Subcutaneous Tissue Disorders: Alopecia

7 DRUG INTERACTIONS
7.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation in Adult Patients
The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

In patients with moderate renal impairment (CrCl 30-50 mL/min), reduce the dosage of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitors dronedarone or systemic ketoconazole. The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dosage adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

7.2 Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients

Avoid use of PRADAXA and P-gp inhibitors in patients with CrCl < 50 mL/min *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

7.3 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Adult Patients Following Hip Replacement Surgery

In patients with CrCl ≥ 50 mL/min who have concomitant administration of P-gp inhibitors such as dronedarone or systemic ketoconazole, it may be helpful to separate the timing of administration of PRADAXA and the P-gp inhibitor by several hours. The concomitant use of PRADAXA and P-gp inhibitors in patients with CrCl < 50 mL/min should be avoided *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.2, 12.3)]*.

7.4 Treatment and Reduction in Risk of Recurrence of VTE in Pediatric Patients

The concomitant use of PRADAXA with P-gp inhibitors has not been studied in pediatric patients but may increase exposure to dabigatran *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on PRADAXA use in pregnant women are insufficient to determine drug-associated risks for adverse developmental outcomes. There are risks to the mother associated with untreated venous thromboembolism in pregnancy and a risk of hemorrhage in the mother and fetus associated with the use of anticoagulants *(see Clinical Considerations)*. In pregnant rats treated from implantation until weaning, dabigatran increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition at an exposure 2.6 times the human exposure. At a similar exposure, dabigatran decreased the number of implantations when rats were treated prior to mating and up to implantation (gestation Day 6). Dabigatran administered to pregnant rats and rabbits during organogenesis up to exposures 8 and 13 times the human exposure, respectively, did not induce major malformations. However, the incidence of delayed or irregular ossification of fetal skull bones and vertebrae was increased in the rat *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk for thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reaction

Use of anticoagulants, including PRADAXA, may increase the risk of bleeding in the fetus and neonate. Monitor neonates for bleeding *[see Warnings and Precautions (5.2)]*.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. PRADAXA use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider discontinuation or use of shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions (5.2, 5.3)]*.

Data

Animal Data

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Dabigatran administered to pregnant rats and rabbits during organogenesis up to maternally toxic doses of 200 mg/kg (8 and 13 times the human exposure, respectively, at a MRHD of 300 mg/day based on AUC comparisons) did not induce major malformations, but increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat.

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.2 Lactation

Risk Summary

There are insufficient data to assess the presence of dabigatran in human milk. There are no data on the effects of dabigatran on the breastfed child or on milk production. Dabigatran and/or its metabolites were present in rat milk. Breastfeeding is not recommended during treatment with PRADAXA.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including PRADAXA should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use
The safety and effectiveness of PRADAXA Capsules for the treatment and the reduction in risk of recurrence of venous thromboembolism have been established in pediatric patients 8 to less than 18 years of age. Use of PRADAXA for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients. These studies included an open-label, randomized, parallel-group study and an open-label, single-arm safety study *[see Adverse Reactions (6.1) and Clinical Studies (14.4, 14.5)]*. Other age-appropriate pediatric dosage forms of dabigatran etexilate are available for pediatric patients less than 8 years of age for these indications.

Safety and effectiveness of PRADAXA Capsules have not been established in pediatric patients with non-valvular atrial fibrillation or those who have undergone hip replacement surgery.

8.5 Geriatric Use
Of the total number of patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups *[see Warnings and Precautions (5), Adverse Reactions (6.1), and Clinical Studies (14.1)]*.

8.6 Renal Impairment
Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation in Adult Patients
No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment *[see Clinical Pharmacology (12.3)]*. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Dosage and Administration (2.2, 2.4) and Clinical Pharmacology (12.3)]*. Dosing recommendations for patients with CrCl < 15 mL/min or on dialysis cannot be provided.

Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors *[see Warnings and Precautions (5.5), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients
Patients with severe renal impairment (CrCl ≤ 30 mL/min) were excluded from RE-COVER.

Dosing recommendations for patients with CrCl ≤ 30 mL/min or on dialysis cannot be provided. Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl < 50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Adult Patients Following Hip Replacement Surgery
Patients with severe renal impairment (CrCl < 30 mL/min) were excluded from RE-NOVATE and RE-NOVATE II.

Dosing recommendations for patients with CrCl < 30 mL/min or on dialysis cannot be provided.

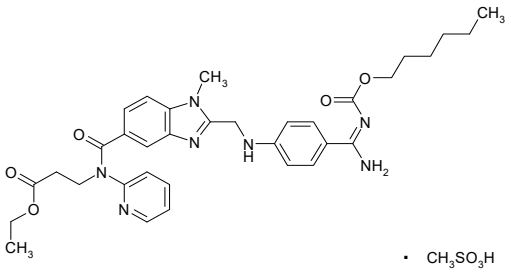
Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl < 50 mL/min *[see Warnings and Precautions (5.5), Drug Interactions (7.3), and Clinical Pharmacology (12.2, 12.3)]*.

Treatment and Reduction in the Risk of Recurrence of VTE in Pediatric Patients
PRADAXA has not been studied in pediatric patients with eGFR < 50 mL/min/1.73 m^2. Reduced renal function could increase exposure. Dosing recommendations cannot be provided for treatment of these patients. Avoid use of PRADAXA Capsules in these patients *[see Dosage and Administration (2.4)]*.

10 OVERDOSAGE
Accidental overdose may lead to hemorrhagic complications. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. A specific reversal agent (idarucizumab) is available for adult patients.

Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

11 DESCRIPTION
The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

PRADAXA Capsules are supplied in 75 mg, 110 mg, and 150 mg strengths for oral administration. Each capsule contains dabigatran etexilate mesylate as the active ingredient: 150 mg dabigatran etexilate (equivalent to 172.95 mg dabigatran etexilate mesylate), 110 mg dabigatran etexilate (equivalent to 126.83 mg dabigatran

etexilate mesylate), or 75 mg dabigatran etexilate (equivalent to 86.48 mg dabigatran etexilate mesylate) along with the following inactive ingredients: acacia, dimethicone, hydroxypropyl cellulose, hypromellose, talc, and tartaric acid. The capsule shell is composed of black edible ink, carrageenan, FD&C Blue No. 2 (150 mg and 110 mg capsules only), hypromellose, potassium chloride, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

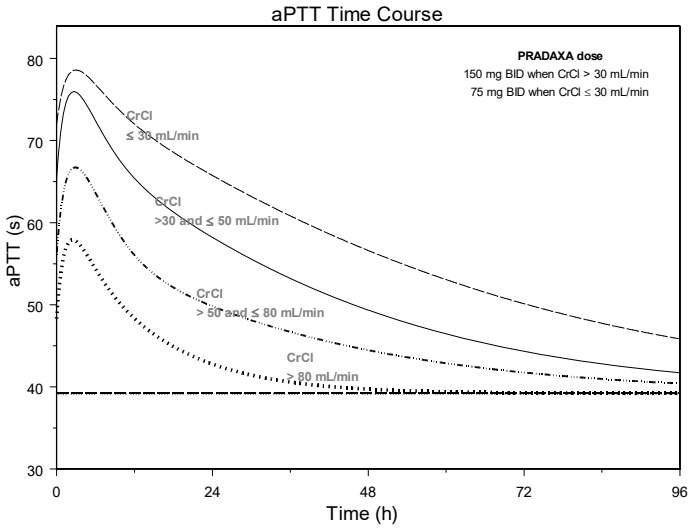
12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, TT, and dTT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring.

Adults

The aPTT test provides an approximation of PRADAXA's anticoagulant effect. The average time course for effects on aPTT, following approved dosing regimens in patients with various degrees of renal impairment is shown in Figure 2. The curves represent mean levels without confidence intervals; variations should be expected when measuring aPTT. While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, the curves can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of PRADAXA is not precisely known. In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds.

Figure 2 Average Time Course for Effects of Dabigatran on aPTT, Following Approved PRADAXA Dosing Regimens in Adult Patients with Various Degrees of Renal Impairment*



*Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RE-LY study; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Roche Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between various established methods for aPTT assessment.

The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than activated partial thromboplastin time (aPTT). In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds.

In orthopedic hip surgery patients, maximum aPTT response (E_{max}) to dabigatran and baseline aPTT were higher shortly after surgery than at later time points (e.g. ≥ 3 days after surgery).

Pediatrics

As in adults, there is a correlation between plasma dabigatran concentrations and the degree of its anticoagulant effect in pediatric patients with venous thromboembolism. The parameters dTT and ECT increased in direct linear proportion to the plasma concentration of dabigatran, whereas aPTT prolongation increases in a nonlinear fashion with dabigatran plasma concentrations.

Similar PK/PD relationships for aPTT, ECT, and dTT were observed across age groups of pediatric patients (ages 26 days to < 18 years) and between pediatric and adult patients with venous thromboembolism. This similarity in PK/PD relationship suggests that similar exposure-response relationship is expected for dabigatran etexilate treatment across the pediatric age groups and adult patients.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy adult subjects and adult patients in the range of doses from 10 to 400 mg. Given twice daily, dabigatran's accumulation factor in adults and pediatrics is approximately two.

Absorption
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3% to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1-hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation based on a single-dose relative bioavailability study. PRADAXA Capsules should therefore not be broken, chewed, or opened before administration.

PRADAXA is available in capsules and oral pellets. The approved indications and intended age groups are not the same. Oral absorption of dabigatran etexilate is formulation-dependent. At steady-state, dabigatran etexilate oral pellets show 37% higher relative bioavailability in healthy adults compared to dabigatran etexilate capsules based on a multiple-dose relative bioavailability study. In addition, the relative bioavailability between the two dosage forms is age-dependent. The relative bioavailability observed in adults cannot be translated to pediatrics.

Distribution
Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L.

Elimination
Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy adult subjects is 12 to 17 hours. Population pharmacokinetic simulation shows that the elimination half-life in pediatric patients is 12 to 14 hours.

Metabolism
After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation, forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Specific Populations
Pediatric Patients
The pharmacokinetics of dabigatran was characterized in two clinical studies (DIVERSITY and Study 2) following multiple doses in pediatric patients from birth to less than 18 years old. In pediatric patients taking age- and weight-adjusted dosages of PRADAXA Capsules (aged 8-18 years), the observed geometric mean steady-state trough concentration was 97.9 ng/mL (63.7 to 151 ng/mL, 10^{th} to 90^{th} percentile) compared to the steady-state geometric mean trough concentration of 59.7 ng/mL (26.3 to 146 ng/mL, 10^{th} to 90^{th} percentile) observed in adult patients with DVT/PE.

Renal Impairment
An open, parallel-group, single-center study compared dabigatran pharmacokinetics in healthy adult subjects and adult patients with mild to moderate renal impairment receiving a single dose of PRADAXA Capsules 150 mg. Exposure to dabigatran increases with severity of renal function impairment (Table 10). Similar findings were observed in the RE-LY, RE-COVER and RE-NOVATE II trials.

Table 10 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	≥ 80	1x	1x	13
Mild	50-80	1.5x	1.1x	15
Moderate	30-50	3.2x	1.7x	18
Severe[+]	15-30	6.3x	2.1x	27

[+]Patients with severe renal impairment were not studied in RE-LY, RE-COVER and RE-NOVATE II. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling *[see Dosage and Administration (2.2, 2.4) and Use in Specific Populations (8.6)]*.

Hepatic Impairment
Administration of PRADAXA Capsules in adult patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics.

Drug Interactions
A summary of the effect of coadministered drugs on dabigatran exposure in healthy adult subjects is shown in Figures 3.1 and 3.2.

In the orthopedic hip surgery patients, limited clinical data with P-gp inhibitors is available.

Figure 3.1 Effect of P-gp Inhibitor or Inducer (rifampicin) Drugs on Peak and Total Exposure to Dabigatran (C_{max} and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dosage and Dosage Frequency are given as well as the Time of Perpetrator Dosage in Relation to Dabigatran Etexilate Dosage (Time Difference)

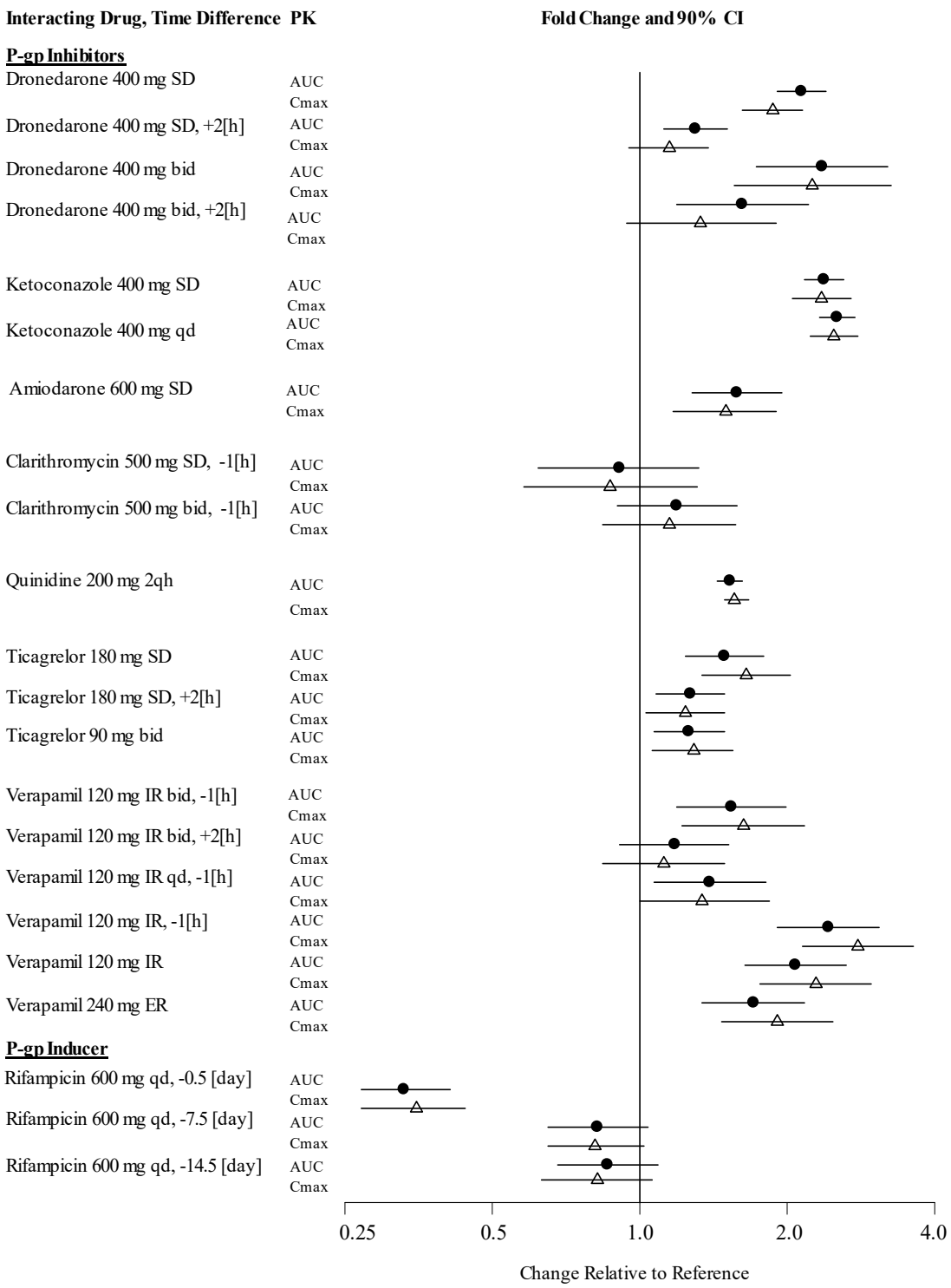
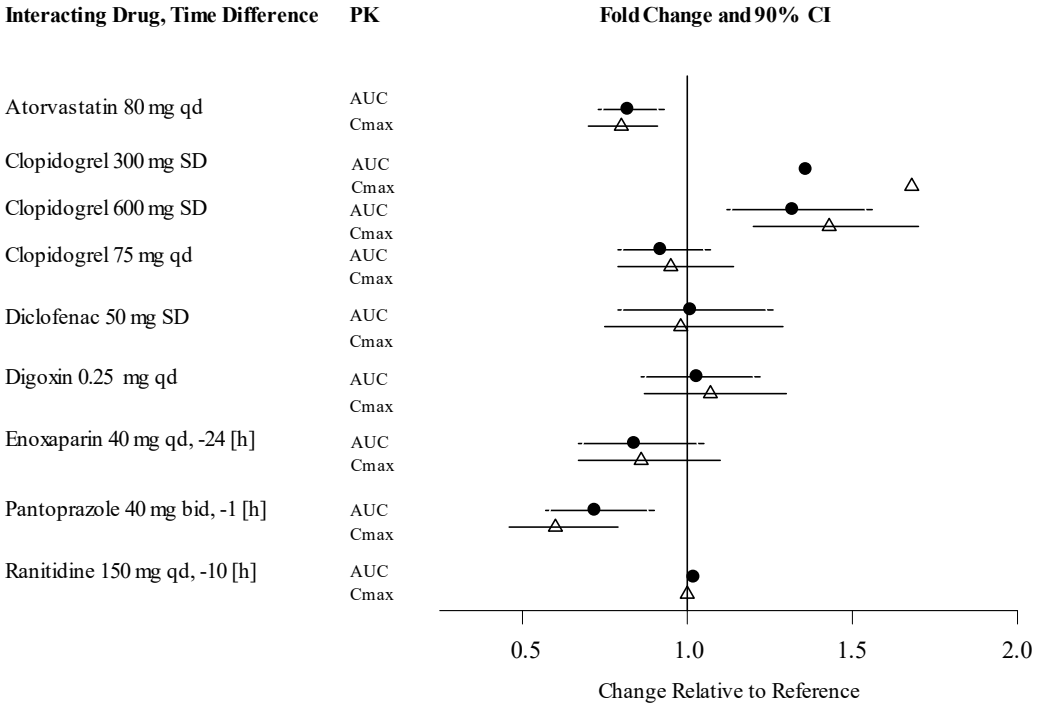


Figure 3.2 Effect of Non-P-gp Inhibitor or Inducer, Other Drugs, on Peak and Total Exposure to Dabigatran (C_{max} and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dosage and Dosage Frequency are given as well as the Time of Perpetrator Dosage in Relation to Dabigatran Etexilate Dosage (Time Difference)



In RE-LY, dabigatran plasma samples were also collected. The concomitant use of proton pump inhibitors, H2 antagonists, and digoxin did not appreciably change the trough concentration of dabigatran.

Impact of Dabigatran on Other Drugs
In clinical studies exploring CYP3A4, CYP2C9, P-gp and other pathways, dabigatran did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation in Adult Patients

The clinical evidence for the efficacy of PRADAXA Capsules was derived from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), a multi-center, multi-national, randomized, parallel group trial comparing two blinded dosages of PRADAXA Capsules (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more of the following additional risk factors:

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

The primary objective of this study was to determine if PRADAXA Capsules was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolism. The study was designed to ensure that PRADAXA Capsules preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

A total of 18,113 patients were randomized and followed for a median of 2 years. The patients' mean age was 71.5 years and the mean $CHADS_2$ score was 2.1. The patient population was 64% male, 70% Caucasian, 16% Asian, and 1% black. Twenty percent of patients had a history of a stroke or TIA and 50% were vitamin K antagonist (VKA) naïve, defined as less than 2 months total lifetime exposure to a VKA. Thirty-two percent of the population had never been exposed to a VKA. Concomitant diseases of patients in this trial included hypertension 79%, diabetes 23%, and CAD 28%. At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%.

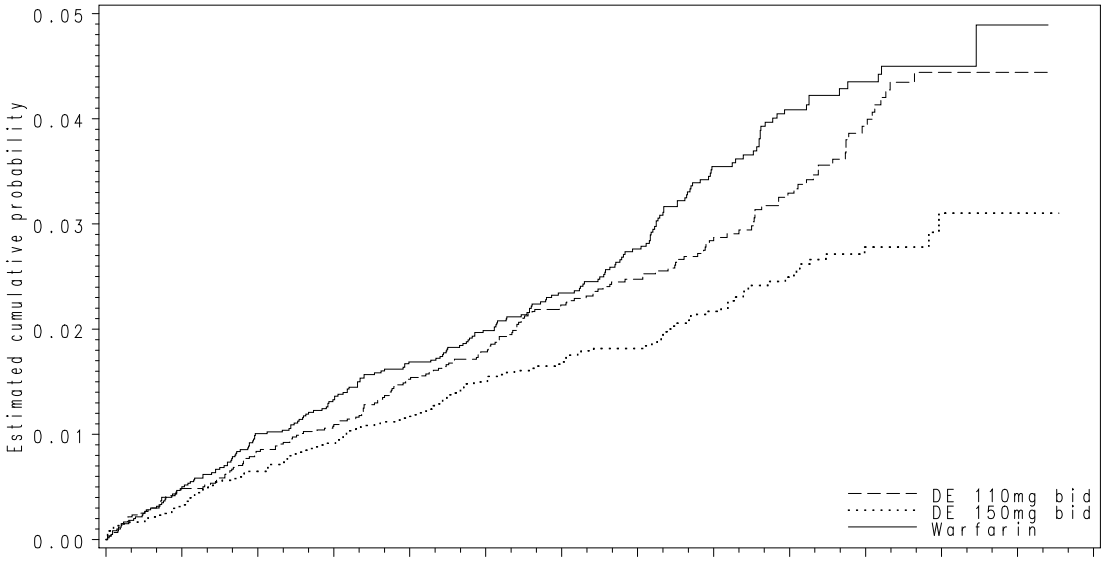
Relative to warfarin and to PRADAXA Capsules 110 mg twice daily, PRADAXA Capsules 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 11 and Figure 4).

Table 11 First Occurrence of Stroke or Systemic Embolism in the RE-LY Study*

	PRADAXA Capsules 150 mg twice daily	**PRADAXA Capsules 110 mg twice daily**	**Warfarin**
Patients randomized	6,076	6,015	6,022
Patients (% per yr) with events	135 (1.12%)	183 (1.54%)	203 (1.72%)
Hazard ratio vs warfarin (95% CI)	0.65 (0.52, 0.81)	0.89 (0.73, 1.09)	
P-value for superiority	0.0001	0.27	
Hazard ratio vs PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.91)		
P-value for superiority	0.005		

* Randomized ITT

Figure 4 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



Subjects at risk													
DE 110mg bid	6015	5927	5862	5797	5713	5481	4615	3778	3132	2386	1446	495	87
DE 150mg bid	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3091	2338	1364	383	76

The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 12. The treatment effect was primarily a reduction in stroke. PRADAXA Capsules 150 mg twice daily was superior in reducing ischemic and hemorrhagic strokes relative to warfarin.

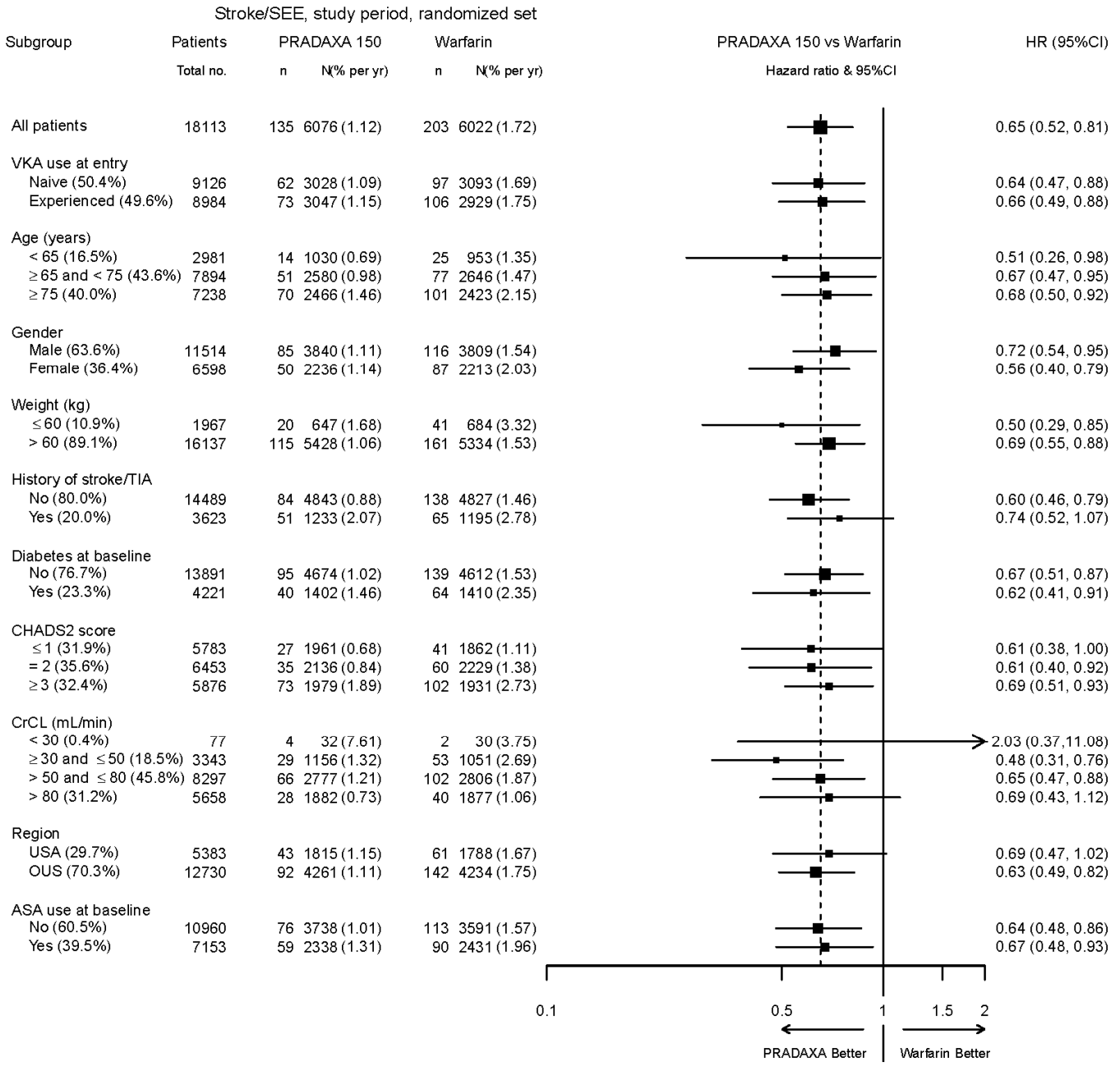
Table 12 Strokes and Systemic Embolism in the RE-LY Study

	PRADAXA Capsules 150 mg twice daily	**Warfarin**	**Hazard ratio vs warfarin (95% CI)**
Patients randomized	6,076	6,022	
Stroke	123	187	0.64 (0.51, 0.81)
Ischemic stroke	104	134	0.76 (0.59, 0.98)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

In the RE-LY trial, the rate of all-cause mortality was lower on PRADAXA Capsules 150 mg than on warfarin (3.6% per year versus 4.1% per year). The rate of vascular death was lower on PRADAXA Capsules 150 mg compared to warfarin (2.3% per year versus 2.7% per year). Non-vascular death rates were similar in the treatment arms.

The efficacy of PRADAXA Capsules 150 mg twice daily was generally consistent across major subgroups (see Figure 5).

Figure 5 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics*



* Randomized ITT

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

In RE-LY, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA Capsules (0.7 per 100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

14.2 Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism in Adult Patients

In the randomized, parallel group, double-blind trials, RE-COVER and RE-COVER II, patients with deep vein thrombosis and pulmonary embolism received PRADAXA Capsules 150 mg twice daily or warfarin (dosed to target INR of 2 to 3) following initial treatment with an approved parenteral anticoagulant for 5 to 10 days.

In RE-COVER, the median treatment duration during the oral only treatment period was 174 days. A total of 2,539 patients (30.9% patients with symptomatic PE with or without DVT and 68.9% with symptomatic DVT only) were treated with a mean age of 54.7 years. The patient population was 58.4% male, 94.8% white, 2.6% Asian, and 2.6% black. The concomitant diseases of patients in this trial included hypertension (35.9%), diabetes mellitus (8.3%), coronary artery disease (6.5%), active cancer (4.8%), and gastric or duodenal ulcer (4.4%). Concomitant medications included agents acting on renin-angiotensin system (25.2%), vasodilators (28.4%), serum

lipid-reducing agents (18.2%), NSAIDs (21%), beta-blockers (14.8%), calcium channel blockers (8.5%), ASA (8.6%), and platelet inhibitors excluding ASA (0.6%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 60% in RE-COVER study.

In RE-COVER II, the median treatment duration during the oral only treatment period was 174 days. A total of 2,568 patients (31.8% patients with symptomatic PE with or without DVT and 68.1% with symptomatic DVT only) were treated with a mean age of 54.9 years. The patient population was 60.6% male, 77.6% white, 20.9% Asian, and 1.5% black. The concomitant diseases of patients in this trial included hypertension (35.1%), diabetes mellitus (9.8%), coronary artery disease (7.1%), active cancer (3.9%), and gastric or duodenal ulcer (3.8%). Concomitant medications included agents acting on renin-angiotensin system (24.2%), vasodilators (28.6%), serum lipid-reducing agents (20.0%), NSAIDs (22.3%), beta-blockers (14.8%), calcium channel blockers (10.8%), ASA (9.8%), and platelet inhibitors excluding ASA (0.8%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 57% in RE-COVER II study.

In studies RE-COVER and RE-COVER II, the protocol specified non-inferiority margin (2.75) for the hazard ratio was derived based on the upper limit of the 95% confidence interval of the historical warfarin effect. PRADAXA Capsules was demonstrated to be non-inferior to warfarin (dosed to target INR of 2 to 3) (Table 13) based on the primary composite endpoint (fatal PE or symptomatic non-fatal PE and/or DVT) and retains at least 66.9% (RE-COVER) and 63.9% (RE-COVER II) of the historical warfarin effect, respectively.

Table 13 Primary Efficacy Endpoint for RE-COVER and RE-COVER II – Modified ITT[a] Population

	PRADAXA Capsules 150 mg twice daily N (%)	Warfarin N (%)	Hazard ratio vs warfarin (95% CI)
RE-COVER	**N=1,274**	**N=1,265**	
Primary Composite Endpoint[b]	34 (2.7)	32 (2.5)	1.05 (0.65, 1.70)
Fatal PE[c]	1 (0.1)	3 (0.2)	
Symptomatic non-fatal PE[c]	16 (1.3)	8 (0.6)	
Symptomatic recurrent DVT[c]	17 (1.3)	23 (1.8)	
RE-COVER II	**N=1,279**	**N=1,289**	
Primary Composite Endpoint[b]	34 (2.7)	30 (2.3)	1.13 (0.69, 1.85)
Fatal PE[c]	3 (0.2)	0	
Symptomatic non-fatal PE[c]	9 (0.7)	15 (1.2)	
Symptomatic recurrent DVT[c]	30 (2.3)	17 (1.3)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more event.
[c]Number of events. For patients with multiple events each event is counted independently.

In the randomized, parallel-group, double-blind, pivotal trial, RE-MEDY, patients received PRADAXA Capsules 150 mg twice daily or warfarin (dosed to target INR of 2 to 3) following 3 to 12 months of treatment with anticoagulation therapy for an acute VTE. The median treatment duration during the treatment period was 534 days. A total of 2,856 patients were treated with a mean age of 54.6 years. The patient population was 61% male, and 90.1% white, 7.9% Asian and 2.0% black. The concomitant diseases of patients in this trial included hypertension (38.6%), diabetes mellitus (9.0%), coronary artery disease (7.2%), active cancer (4.2%), and gastric or duodenal ulcer (3.8%). Concomitant medications included agents acting on renin-angiotensin system (27.9%), vasodilators (26.7%), serum lipid reducing agents (20.6%), NSAIDs (18.3%), beta-blockers (16.3%), calcium channel blockers (11.1%), aspirin (7.7%), and platelet inhibitors excluding ASA (0.9%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 62% in the study.

In study RE-MEDY, the protocol specified non-inferiority margin (2.85) for the hazard ratio was derived based on the point estimate of the historical warfarin effect. PRADAXA Capsules was demonstrated to be non-inferior to warfarin (dosed to target INR of 2 to 3) (Table 14) based on the primary composite endpoint (fatal PE or symptomatic non-fatal PE and/or DVT) and retains at least 63.0% of the historical warfarin effect. If the non-inferiority margin was derived based on the 50% retention of the upper limit of the 95% confidence interval, PRADAXA Capsules was demonstrated to retain at least 33.4% of the historical warfarin effect based on the composite primary endpoint.

Table 14 Primary Efficacy Endpoint for RE-MEDY – Modified ITT[a] Population

	PRADAXA Capsules 150 mg twice daily N=1,430 N (%)	Warfarin N=1,426 N (%)	Hazard ratio vs warfarin (95% CI)
Primary Composite Endpoint[b]	26 (1.8)	18 (1.3)	1.44 (0.78, 2.64)
Fatal PE[c]	1 (0.07)	1 (0.07)	
Symptomatic non-fatal PE[c]	10 (0.7)	5 (0.4)	
Symptomatic recurrent DVT[c]	17 (1.2)	13 (0.9)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.
[b]Number of patients with one or more event.
[c]Number of events. For patients with multiple events each event is counted independently.

In a randomized, parallel-group, double-blind, pivotal trial, RE-SONATE, patients received PRADAXA Capsules 150 mg twice daily or placebo following 6 to 18 months of treatment with anticoagulation therapy for an acute VTE. The median treatment duration was 182 days. A total of 1,343 patients were treated with a mean age of 55.8 years. The patient population was 55.5% male, 89.0% white, 9.3% Asian, and 1.7% black. The concomitant diseases of patients in this trial included

hypertension (38.8%), diabetes mellitus (8.0%), coronary artery disease (6.0%), history of cancer (6.0%), gastric or duodenal ulcer (4.5%), and heart failure (4.6%). Concomitant medications included agents acting on renin-angiotensin system (28.7%), vasodilators (19.4%), beta-blockers (18.5%), serum lipid reducing agents (17.9%), NSAIDs (12.1%), calcium channel blockers (8.9%), aspirin (8.3%), and platelet inhibitors excluding ASA (0.7%). Based on the outcome of the primary composite endpoint (fatal PE, unexplained death, or symptomatic non-fatal PE and/or DVT), PRADAXA was superior to placebo (Table 15).

Table 15 Primary Efficacy Endpoint for RE-SONATE – Modified ITT[a] Population

	PRADAXA Capsules 150 mg twice daily N=681 N (%)	**Placebo N=662 N (%)**	**Hazard ratio vs placebo (95% CI)**
Primary Composite Endpoint[b]	3 (0.4)	37 (5.6)	0.08 (0.02, 0.25) p-value <0.0001
Fatal PE and unexplained death[c]	0	2 (0.3)	
Symptomatic non-fatal PE[c]	1 (0.1)	14 (2.1)	
Symptomatic recurrent DVT[c]	2 (0.3)	23 (3.5)	

[a]Modified ITT analyses population consists of all randomized patients who received at least one dose of study medication.

[b]Number of patients with one or more events.

[c]Number of events. For patients with multiple events each event is counted independently.

14.3 Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism in Adult Patients Following Hip Replacement Surgery

In the randomized, parallel-group, double-blind, non-inferiority trials, RE-NOVATE and RE-NOVATE II patients received PRADAXA Capsules 75 mg orally 1-4 hours after surgery followed by 150 mg daily (RE-NOVATE), PRADAXA Capsules 110 mg orally 1-4 hours after surgery followed by 220 mg daily (RE-NOVATE and RE-NOVATE II) or subcutaneous enoxaparin 40 mg once daily initiated the evening before surgery (RE-NOVATE and RE-NOVATE II) for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients who have undergone hip replacement surgery.

Overall, in RE-NOVATE and RE-NOVATE II, the median treatment duration was 33 days for PRADAXA Capsules and 33 days for enoxaparin. A total of 5,428 patients were treated with a mean age of 63.2 years. The patient population was 45.3% male, 96.1% white, 3.6% Asian, and 0.4 % black. The concomitant diseases of patients in these trials included hypertension (46.1%), venous insufficiency (15.4%), coronary artery disease (8.2%), diabetes mellitus (7.9%), reduced renal function (5.3%), heart failure (3.4%), gastric or duodenal ulcer (3.0%), VTE (2.7%), and malignancy (0.1%). Concomitant medications included cardiac therapy (69.7%), NSAIDs (68%), vasoprotectives (29.7%), agents acting on renin-angiotensin system (29.1%), beta-blockers (21.5%), diuretics (20.8%), lipid modifying agents (18.2%), any antithrombin/anticoagulant (16.0%), calcium channel blockers (13.6%), low molecular weight heparin (7.8%), aspirin (7.0%), platelet inhibitors excluding ASA (6.9%), other antihypertensives (6.7%), and peripheral vasodilators (2.6%).

For efficacy evaluation all patients were to have bilateral venography of the lower extremities at 3 days after last dose of study drug unless an endpoint event had occurred earlier in the study. In the primary efficacy analysis, PRADAXA Capsules 110 mg orally 1-4 hours after surgery followed by 220 mg daily was non-inferior to enoxaparin 40 mg once daily in a composite endpoint of confirmed VTE (proximal or distal DVT on venogram, confirmed symptomatic DVT, or confirmed PE) and all cause death during the treatment period (Tables 16 and 17). In the studies 2628 (76.5%) patients in RE-NOVATE and 1572 (78.9%) patients in RE-NOVATE II had evaluable venograms at study completion.

Table 16 Primary Efficacy Endpoint for RE-NOVATE

	PRADAXA Capsules 220 mg N (%)	**Enoxaparin N (%)**
Number of Patients[a]	**N=880**	**N= 897**
Primary Composite Endpoint	53 (6.0)	60 (6.7)
Risk difference (%) vs enoxaparin (95% CI)	-0.7 (-2.9, 1.6)	
Number of Patients	**N=909**	**N=917**
Composite endpoint of major VTE[b] and VTE related mortality	28 (3.1)	36 (3.9)
Number of Patients	**N=905**	**N=914**
Proximal DVT	23 (2.5)	33 (3.6)
Number of Patients	**N=874**	**N=894**
Total DVT	46 (5.3)	57 (6.4)
Number of Patients	**N=1,137**	**N=1,142**
Symptomatic DVT	6 (0.5)	1 (0.1)
PE	5 (0.4)	3 (0.3)
Death	3 (0.3)	0

[a]Full Analysis Set (FAS): The FAS included all randomized patients who received at least one subcutaneous injection or one oral dose of study medication, underwent surgery and subjects for whom the presence or absence of an efficacy outcome at the end of the study was known, i.e., an evaluable negative venogram for both distal

and proximal DVT in both legs or any of the following: positive venography in one or both legs, or confirmed symptomatic DVT, PE, or death during the treatment period.
[b]VTE is defined as proximal DVT and PE

Table 17 Primary Efficacy Endpoint for RE-NOVATE II

	PRADAXA Capsules 220 mg N (%)	Enoxaparin N (%)
Number of Patients[a]	**N=792**	**N= 786**
Primary Composite Endpoint	61 (7.7)	69 (8.8)
Risk difference (%) vs enoxaparin (95% CI)	-1.1 (-3.8, 1.6)	
Number of Patients	**N=805**	**N=795**
Composite endpoint of major VTE[b] and VTE related mortality	18 (2.2)	33 (4.2)
Number of Patients	**N=804**	**N=793**
Proximal DVT	17 (2.1)	31 (3.9)
Number of Patients	**N=791**	**N=784**
Total DVT	60 (7.6)	67 (8.5)
Number of Patients	**N=1,001**	**N=992**
Symptomatic DVT	0	4 (0.4)
PE	1 (0.1)	2 (0.2)
Death	0	1 (0.1)

[a]Full Analysis Set (FAS): The FAS included all randomized patients who received at least one subcutaneous injection or one oral dose of study medication, underwent surgery and subjects for whom the presence or absence of an efficacy outcome at the end of the study was known, i.e., an evaluable negative venogram for both distal and proximal DVT in both legs or any of the following: positive venography in one or both legs, or confirmed symptomatic DVT, PE, or death during the treatment period.
[b]VTE is defined as proximal DVT and PE

14.4 Treatment of VTE in Pediatric Patients
The DIVERSITY study was conducted to demonstrate the efficacy and safety of PRADAXA compared to standard of care (SOC) for the treatment of venous thromboembolism (VTE) in pediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomized, parallel-group, non-inferiority study. Patients enrolled were randomized according to a 2:1 scheme to either an age-appropriate formulation (capsules, oral pellets, or oral solution) of PRADAXA (doses adjusted for age and weight) after at least 5 days and no longer than 21 days of treatment with a parenteral anticoagulant, or to SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux. For patients on PRADAXA, drug concentration was determined prior to the 7th dose and a single titration was permitted to achieve drug target levels of 50-250 ng/mL. Inability to achieve target, after one up-titration, resulted in premature termination of study drug in 12 patients (6.8%).

The median treatment duration during the treatment period was 85 days. In total, 267 patients entered the study (leading index VTE was 64% deep vein thrombosis, 10% cerebral venous thrombosis or sinus thrombosis, and 9.0% pulmonary embolism), with 18% of patients having a central line-associated thrombosis. The patient population was 49.8% male, 91.8% white, 4.9% Asian, and 1.5% black; 168 patients were 12 to < 18 years old, 64 patients 2 to < 12 years, and 35 patients were younger than 2 years. The concomitant VTE-related risk factors of patients in this trial among study arms were as follows: inherited thrombophilia disorder (PRADAXA: 20%, SOC: 22%), congenital heart disease (PRADAXA: 12%, SOC: 30%), heart failure (PRADAXA: 3%, SOC: 18%), history of cancer (PRADAXA: 10%, SOC: 1%), CVL insertion (PRADAXA: 23%, SOC: 27%), immobility (PRADAXA: 13%, SOC: 10%) and significant infection (PRADAXA: 15%, SOC: 13%). The number of patients taking concomitant medications with hemostatic effects were similar in both treatment groups (PRADAXA: 15%, SOC: 16%).

The efficacy of PRADAXA was established based on a composite endpoint of patients with complete thrombus resolution, freedom from recurrent venous thromboembolic event, and freedom from mortality related to venous thromboembolic event (composite primary endpoint). Of the 267 randomized patients, 81 patients (45.8%) in the PRADAXA group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint. The corresponding rate difference and 95% CI was -0.038 (-0.161, 0.086) and thus demonstrated non-inferiority of PRADAXA to SOC, since the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 20% (see Table 18).

Table 18: Efficacy Results [ITT population] DIVERSITY Study

	PRADAXA	Standard of Care
Number of patients randomized (%)	177 (100.0)	90 (100.0)
Complete thrombus resolution	81 (45.8)	38 (42.2)
Freedom from recurrent VTE	170 (96.0)	83 (92.2)
Freedom from mortality related to VTE	177 (100.0)	89 (98.9)
Composite endpoint met	81 (45.8)	38 (42.2)
Difference in rate (95% CI)[1]	-0.038 (-0.161, 0.086)	
p-value for non-inferiority	< 0.0001	
p-value for superiority	0.2739	

[1] Mantel-Haenszel weighted difference with age group as stratification factor

Subgroup analyses showed that there were no outliers in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors (central venous line, congenital heart disease, malignant disease). For the 3 different age strata, the proportions of patients that met the efficacy endpoint in the PRADAXA and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to < 2 years [Rate Difference -0.052; (95%CI: -0.393, 0.288)], 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to < 12 years [Rate Difference 0.083; (95%CI: -0.176, 0.342)], and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to < 18 years [Rate Difference -0.080; (95%CI: -0.234, 0.074)].

14.5 Reduction in the Risk of Recurrence of VTE in Pediatric Patients

Study 2 was an open-label, single-arm safety study to assess the safety of PRADAXA for the prevention of recurrent VTE in pediatric patients from birth to < 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were included in the study. Eligible patients received age- and weight adjusted dosages of an age-appropriate formulation (capsules or oral pellets) of PRADAXA until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events, and mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months.

Of the 214 patients in the study, 162 patients were 12 to < 18 years old, 43 patients were 2 to < 12 years old, and 9 patients were aged 6 months to < 2 years old.

The overall probability of being free from recurrence of VTE during the on-treatment period was 0.990 (95% CI: 0.960, 0.997) at 3 months, 0.984 (95% CI: 0.950, 0.995) at 6 months, and 0.984 (95% CI: 0.950, 0.995) at 12 months. The probability of being free from bleeding events during the on-treatment period was 0.849 (95% CI: 0.792, 0.891) at 3 months, 0.785 (95% CI: 0.718, 0.838) at 6 months, and 0.723 (95% CI: 0.645, 0.787) at 12 months. No on-treatment deaths occurred.

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 75 mg capsules have a white opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with “R75”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0355-09 Unit of use bottle of 60 capsules
- NDC 0597-0355-56 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 110 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted with “R110”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0108-54 Unit of use bottle of 60 capsules
- NDC 0597-0108-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a white opaque body imprinted with “R150”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0360-55 Unit of use bottle of 60 capsules
- NDC 0597-0360-82 Blister package containing 60 capsules (10 x 6 capsule blister cards)

Bottles

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Once opened, the product must be used within 4 months. Keep the bottle tightly closed. Store in the original package to protect from moisture.

Blisters

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Instructions for Patients

- Tell patients to take PRADAXA Capsules exactly as prescribed.
- Remind patients not to discontinue PRADAXA Capsules without talking to the healthcare provider who prescribed it.
- Keep PRADAXA Capsules in the original bottle to protect from moisture. Do not put PRADAXA Capsules in pill boxes or pill organizers.
- When more than one bottle is dispensed to the patient, instruct them to open only one bottle at a time.
- Instruct patient to remove only one capsule from the opened bottle at the time of use. The bottle should be immediately and tightly closed.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone.
- Advise patients that the capsule should be taken with a full glass of water.

[see Boxed Warning, Dosage and Administration (2.5)]

Bleeding

Inform patients that they may bleed more easily, may bleed longer, and should call their healthcare provider for any signs or symptoms of bleeding *[see Warnings and Precautions (5.2)]*.

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their healthcare provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums

- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

Gastrointestinal Adverse Reactions
Instruct patients to call their healthcare provider if they experience any signs or symptoms of dyspepsia or gastritis:
- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

[see Adverse Reactions (6.1)]

Invasive or Surgical Procedures
Instruct patients to inform their healthcare provider that they are taking PRADAXA before any invasive procedure (including dental procedures) is scheduled *[see Dosage and Administration (2.8)]*.

Concomitant Medications
Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their healthcare provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs) or dabigatran exposure (e.g., dronedarone or systemic ketoconazole) *[see Warnings and Precautions (5.2, 5.5)]*.

Prosthetic Heart Valves
Instruct patients to inform their healthcare provider if they will have or have had surgery to place a prosthetic heart valve *[see Warnings and Precautions (5.4)]*.

Allergic Reactions
Advise adult patients and caregivers that some adults taking PRADAXA have developed symptoms of an allergic reaction. Advise adult patients or caregivers to inform their healthcare provider if they or their child develop symptoms of an allergic reaction, such as hives, rash, or itching. Advise adult patients or caregivers to seek emergency medical attention if they or their child develop chest pain or tightness, swelling of the face or tongue, trouble breathing or wheezing, or feeling dizzy or faint.

Pregnancy
Advise patients to inform their healthcare provider immediately if they become pregnant or intend to become pregnant during treatment with PRADAXA Capsules *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients not to breastfeed if they are taking PRADAXA Capsules *[see Use in Specific Populations (8.2)]*.

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MEDICATION GUIDE
PRADAXA (pra dax a)
(dabigatran etexilate)
Capsules

This Medication Guide is for PRADAXA Capsules. If your healthcare provider prescribes PRADAXA Oral Pellets for you, read the Medication Guide that comes with your medicine.
Read this Medication Guide before you start taking PRADAXA Capsules and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PRADAXA?

- People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. PRADAXA lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking PRADAXA, you may have increased risk of forming a clot in your blood.

  Do not stop taking PRADAXA Capsules without talking to the healthcare provider who prescribes it for you. Stopping PRADAXA increases your risk of having a stroke.

  PRADAXA may need to be stopped, if possible, before surgery or a medical or dental procedure. Ask the healthcare provider who prescribed PRADAXA for you when you should stop taking it. Your healthcare provider will tell you when you may start taking PRADAXA again after your surgery or procedure. If you have to stop taking PRADAXA, your healthcare provider may prescribe another medicine to help prevent a blood clot from forming.

- PRADAXA can cause bleeding which can be serious, and sometimes lead to death. This is because PRADAXA is a blood thinner medicine that lowers the chance of blood clots forming in your body.
- **You may have a higher risk of bleeding if you take PRADAXA and:**
  - are over 75 years old
  - have kidney problems
  - have stomach or intestine bleeding that is recent or keeps coming back, or you have a stomach ulcer
  - take other medicines that increase your risk of bleeding, including:
    - aspirin or aspirin-containing products
    - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
    - a medicine that contains warfarin sodium
    - a medicine that contains heparin
    - a medicine that contains clopidogrel bisulfate
    - a medicine that contains prasugrel
  - have certain kidney problems and also take a medicine that contains dronedarone or ketoconazole tablets.

  Tell your healthcare provider if you take any of these medicines. Ask your healthcare provider or pharmacist if you are not sure if your medicine is one listed above.
- PRADAXA can increase your risk of bleeding because it lessens the ability of your blood to clot. During treatment with PRADAXA:
  - you may bruise more easily
  - it may take longer for any bleeding to stop

  Call your healthcare provider or get medical help right away if you have any of these signs or symptoms of bleeding:
  - unexpected bleeding or bleeding that lasts a long time, such as:
    - unusual bleeding from the gums
    - nose bleeds that happen often
    - menstrual bleeding or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - pink or brown urine
  - red or black stools (looks like tar)
  - bruises that happen without a known cause or get larger
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - unexpected pain, swelling, or joint pain
  - headaches, feeling dizzy or weak

Take PRADAXA Capsules exactly as prescribed. Do not stop taking PRADAXA Capsules without first talking to the healthcare provider who prescribes it for you. Stopping PRADAXA may increase your risk of a stroke.

- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like PRADAXA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

  If you take PRADAXA and receive spinal anesthesia or have a spinal puncture, your healthcare provider should watch you closely for symptoms of spinal or epidural blood clots. Tell your healthcare provider right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), loss of control of the bowels or bladder (incontinence).

See "What are the possible side effects of PRADAXA?" for more information about side effects.

What is PRADAXA?

PRADAXA is a prescription medicine that is used to:

- **in adults:**
  - reduce the risk of stroke and blood clots in adults who have a medical condition called atrial fibrillation that is not caused by a heart valve problem. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to blood clots forming and increase your risk of a stroke.
  - treat blood clots in the veins of your legs (deep vein thrombosis) and lungs (pulmonary embolism) after you have been treated with an injectable medicine to treat your blood clots for 5 to 10 days.
  - reduce your risk of blood clots from happening again in the veins of your legs (deep vein thrombosis) and lungs (pulmonary embolism) after you have received treatment for blood clots.
  - help prevent blood clots in your legs (venous thrombosis) and lungs (pulmonary embolism) after you have just had hip replacement surgery.
- **in children:**
  - treat blood clots in children 8 years to less than 18 years of age who have received an injectable medicine to treat their blood clots for at least 5 days.
  - reduce the risk of blood clots from happening again in children 8 years to less than 18 years of age who have received treatment for blood clots.

It is not known if PRADAXA Capsules are safe and effective in children with atrial fibrillation not caused by a heart valve problem, or in children who have undergone hip replacement surgery.

Do not take PRADAXA if you:

- currently have certain types of abnormal bleeding. Talk to your healthcare provider before taking PRADAXA if you currently have unusual bleeding.
- have had a serious allergic reaction to any of the ingredients in PRADAXA. See the end of this Medication Guide for a complete list of ingredients in PRADAXA. Ask your healthcare provider if you are not sure.
- have ever had or plan to have a valve in your heart replaced with a mechanical (artificial) prosthetic heart valve

Before taking PRADAXA, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have ever had bleeding problems
- have ever had stomach ulcers
- have antiphospholipid syndrome (APS)
- are pregnant or plan to become pregnant. It is not known if PRADAXA will harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with PRADAXA.

  Females who are able to become pregnant: Talk with your healthcare provider about pregnancy planning during treatment with PRADAXA. Talk with your healthcare provider about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including PRADAXA.
- are breastfeeding or plan to breastfeed. It is not known if PRADAXA passes into your breast milk. You should not breastfeed during treatment with PRADAXA Capsules. Talk to your healthcare provider about the best way to feed your baby during treatment with PRADAXA Capsules.

Tell all of your healthcare providers and dentists that you are taking PRADAXA. They should talk to the healthcare provider who prescribed PRADAXA for you before you have **any** surgery or a medical or dental procedure.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way PRADAXA works. Certain medicines may increase your risk of bleeding. See **"What is the most important information I should know about PRADAXA?"**

Especially tell your healthcare provider if you take a medicine that contains rifampin.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take PRADAXA Capsules?

- PRADAXA comes as capsules and oral pellets. If you have a child who is older than 8 years of age and who is prescribed PRADAXA, your healthcare provider will prescribe the type of PRADAXA that is right for your child.
- Your healthcare provider will decide how long you should take PRADAXA. **Do not stop taking PRADAXA Capsules without first talking with your healthcare provider. Stopping PRADAXA may increase your risk of having a stroke or forming blood clots.**
- **Take PRADAXA Capsules exactly as prescribed by your healthcare provider.**
- If PRADAXA is prescribed for your child, your healthcare provider will determine the correct dose of PRADAXA Capsules for your child based on their weight. Your healthcare provider may increase or decrease your child's dose as they grow during treatment and as needed.
- **In adults:** Take PRADAXA Capsules 2 times a day. If you are taking PRADAXA after hip replacement surgery, take PRADAXA 1 time a day.
- **In children:** Take PRADAXA Capsules 2 times a day. Take 1 dose in the morning and 1 dose in the evening about every 12 hours, at about the same time each day.
- You can take PRADAXA Capsules with or without food. Taking PRADAXA Capsules with food may help if you have an upset stomach.
- Swallow PRADAXA Capsules whole with a full glass of water. Tell your healthcare provider if you or your child are not able to swallow the capsules whole. Do not break, chew, or empty the pellets from the capsule.
- **Do not** run out of PRADAXA Capsules. Refill your prescription before you run out. If you plan to have surgery, or a medical or a dental procedure, tell your healthcare provider and dentist that you are taking PRADAXA. You may have to stop taking PRADAXA for a short time. See **"What is the most important information I should know about PRADAXA?"**
- If you miss a dose of PRADAXA Capsules, take it as soon as you remember. If your next dose is less than 6 hours away, skip the missed dose. Do not take two doses of PRADAXA Capsules at the same time.
- If you take too much PRADAXA Capsules, go to the nearest hospital emergency room or call your healthcare provider.
- Call your healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your healthcare provider may need to check you.
- PRADAXA Capsules come in a bottle or in a blister package.
- Only open 1 bottle of PRADAXA Capsules at a time. Finish your opened bottle of PRADAXA Capsules before opening a new bottle.
- After opening a bottle of PRADAXA Capsules, use within 4 months. See "**How should I store PRADAXA Capsules?**"
- When it is time for you to take a dose of PRADAXA Capsules, only remove your prescribed dose of PRADAXA Capsules from your open bottle or blister package.
- Tightly close your bottle of PRADAXA Capsules right away after you take your dose.

What are the possible side effects of PRADAXA?

PRADAXA can cause serious side effects. See **"What is the most important information I should know about PRADAXA?"**

- **Allergic Reactions.** Some adults taking PRADAXA Capsules have developed symptoms of an allergic reaction.
  - Call your healthcare provider if you or your child gets symptoms of an allergic reaction, such as:
    - hives
    - rash
    - itching
  - **Get medical help right away if you or your child gets any of the following symptoms of a serious allergic reaction with PRADAXA Capsules:**
    - chest pain or chest tightness
    - swelling of your face or tongue
    - trouble breathing or wheezing
    - feeling dizzy or faint

Common side effects of PRADAXA in adults and children include:

- indigestion, upset stomach, or burning
- stomach-area (abdominal) pain or discomfort

In children, common side effects also include:

- nausea, vomiting, or diarrhea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PRADAXA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PRADAXA Capsules?

- Store PRADAXA Capsules at room temperature 68°F to 77°F (20°C to 25°C).
- After opening the bottle, use PRADAXA Capsules within 4 months. Safely throw away any unused PRADAXA Capsules after 4 months.
- **Keep PRADAXA Capsules in the original bottle or blister package to keep them dry (protect the capsules from moisture). Do not put PRADAXA Capsules in pill boxes or pill organizers.**
- **Tightly close your bottle of PRADAXA Capsules right away after you take your dose.**

Keep PRADAXA Capsules and all medicines out of the reach of children.

General information about the safe and effective use of PRADAXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA Capsules for a condition for which it was not prescribed. Do not give PRADAXA Capsules to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about PRADAXA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about PRADAXA that is written for health professionals.

What are the ingredients in PRADAXA Capsules?

Active ingredient: dabigatran etexilate mesylate

Inactive ingredients: acacia, dimethicone, hydroxypropyl cellulose, hypromellose, talc, and tartaric acid. The capsule shell is composed of black edible ink, carrageenan, FD&C Blue No. 2 (150 mg and 110 mg capsules only), hypromellose, potassium chloride, and titanium dioxide.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA

For more information about PRADAXA, including current prescribing information and Medication Guide, go to **www.pradaxa.com** or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or scan the code to go to **www.pradaxa.com**.

COL8774FG192024

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 6/2025

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PRADAXA Oral Pellets safely and effectively. See full prescribing information for PRADAXA Oral Pellets.

PRADAXA® (dabigatran etexilate) oral pellets
Initial U.S. Approval: 2010

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.5, 2.6, 2.7, 5.1).

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.3). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

---------- INDICATIONS AND USAGE----------
PRADAXA Oral Pellets are a direct thrombin inhibitor indicated:
- For the treatment of venous thromboembolic events (VTE) in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days (1.1)
- To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Treatment of Pediatric Venous Thromboembolic Events (VTE):
  - For pediatric patients aged 3 months to less than 2 years: age- and weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant (2.2)
  - For pediatric patients 2 years to less than 12 years: weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant (2.2)
- Reduction in the Risk of Recurrence of Pediatric VTE:
  - For pediatric patients aged 3 months to less than 2 years: age- and weight-based dosage, twice daily after previous treatment (2.2)
  - For pediatric patients aged 2 years to less than 12 years: weight-based dosage, twice daily after previous treatment (2.2)
- Pradaxa Oral Pellets are NOT substitutable on a milligram-to-milligram basis with other dabigatran etexilate dosage forms (2.1)
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.5, 2.6)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.7)

---------- DOSAGE FORMS AND STRENGTHS ----------
Oral pellets: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg per packet (3)

---------- CONTRAINDICATIONS ----------
- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)
- Mechanical prosthetic heart valve (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Bleeding: PRADAXA can cause serious and fatal bleeding (5.2)
- Bioprosthetic heart valves: PRADAXA use not recommended (5.4)
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome: PRADAXA use not recommended (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (> 15%) are gastrointestinal adverse reactions and bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS----------
- P-gp inducers: Avoid coadministration with PRADAXA (5.5)
- The concomitant use of PRADAXA with P-gp inhibitors has not been studied in pediatric patients but may increase exposure to dabigatran (5.5, 7)

---------- USE IN SPECIFIC POPULATIONS ----------
- Lactation: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised:6/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS
Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.5, 2.6, 2.7) and Warnings and Precautions (5.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA
Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of PRADAXA and neuraxial procedures is not known**

***[see Warnings and Precautions (5.3)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of Venous Thromboembolic Events in Pediatric Patients

PRADAXA Oral Pellets are indicated for the treatment of venous thromboembolic events (VTE) in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days.

1.2 Reduction in the Risk of Recurrence of Venous Thromboembolic Events in Pediatric Patients

PRADAXA Oral Pellets are indicated to reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

Dabigatran etexilate is available in different dosage forms and not all dosage forms are approved for the same indications and age groups. In addition, there are differences between the dosage forms with respect to dosing due to differences in bioavailability. Do not substitute different dosage forms (for example, capsules) for oral pellets on a milligram-to-milligram basis and do not combine more than one dosage form to achieve the total dose *[see Clinical Pharmacology (12.3)]*.

2.2 Recommended PRADAXA Oral Pellets Dosage for Pediatric Patients

PRADAXA Oral Pellets can be used in pediatric patients aged 3 months to less than 12 years as soon as they are able to swallow soft food. For the treatment of VTE in pediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For reduction in risk of recurrence of VTE, treatment should be initiated following previous treatment.

The recommended dosage of PRADAXA Oral Pellets is based on the patient's age and actual weight as shown in the tables below. PRADAXA Oral Pellets is administered twice daily. Adjust the dosage according to age and actual weight as treatment progresses.

Table 1 Age- and Weight-Based Dosage for PRADAXA Oral Pellets for Pediatric Patients less than 2 Years Old

Actual Weight (kg)	Age (in months)	Dosage (mg) twice daily	Number of Packets Needed
3 kg to less than 4 kg	3 to less than 6 months	30 mg	one 30 mg packet twice daily
4 kg to less than 5 kg	3 to less than 10 months	40 mg	one 40 mg packet twice daily
5 kg to less than 7 kg	3 to less than 5 months	40 mg	one 40 mg packet twice daily
	5 to less than 24 months	50 mg	one 50 mg packet twice daily
7 kg to less than 9 kg	3 to less than 4 months	50 mg	one 50 mg packet twice daily
	4 to less than 9 months	60 mg	two 30 mg packets twice daily
	9 to less than 24 months	70 mg	one 30 mg packet plus one 40 mg packet twice daily
9 kg to less than 11 kg	5 to less than 6 months	60 mg	two 30 mg packets twice daily
	6 to less than 11 months	80 mg	two 40 mg packets twice daily

Actual Weight (kg)	Age (in months)	Dosage (mg) twice daily	Number of Packets Needed
	11 to less than 24 months	90 mg	one 40 mg packet plus one 50 mg packet twice daily
11 kg to less than 13 kg	8 to less than 18 months	100 mg	two 50 mg packets twice daily
	18 to less than 24 months	110 mg	one 110 mg packet twice daily
13 kg to less than 16 kg	10 to less than 11 months	100 mg	two 50 mg packets twice daily
	11 to less than 24 months	140 mg	one 30 mg packet plus one 110 mg packet twice daily
16 kg to less than 21 kg	12 to less than 24 months	140 mg	one 30 mg packet plus one 110 mg packet twice daily
21 kg to less than 26 kg	18 to less than 24 months	180 mg	one 30 mg packet plus one 150 mg packet twice daily

Table 2 Weight-Based Dosage for PRADAXA Oral Pellets for Pediatric Patients between 2 Years to less than 12 Years Old

Actual Weight (kg)	Dosage (mg) twice daily	Number of Packets Needed
7 kg to less than 9 kg	70 mg	one 30 mg packet plus one 40 mg packet twice daily
9 kg to less than 11 kg	90 mg	one 40 mg packet plus one 50 mg packet twice daily
11 kg to less than 13 kg	110 mg	one 110 mg packet twice daily
13 kg to less than 16 kg	140 mg	one 30 mg packet plus one 110 mg packet twice daily
16 kg to less than 21 kg	170 mg	one 20 mg packet plus one 150 mg packet twice daily
21 kg to less than 41 kg	220 mg	two 110 mg packets twice daily
41 kg or greater	260 mg	one 110 mg packet plus one 150 mg packet twice daily

Evaluation of the extent of anticoagulation in pediatric patients on PRADAXA Oral Pellets may be accomplished using dTT or ECT, and not INR *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

2.3 Dosage Adjustments

Pediatric Patients with Renal Impairment

Assess renal function prior to initiation of treatment with PRADAXA Oral Pellets. Periodically assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly. Discontinue PRADAXA Oral Pellets in patients who develop acute renal failure while on PRADAXA Oral Pellets and consider alternative anticoagulant therapy.

Prior to the initiation of treatment with PRADAXA Oral Pellets, estimate the glomerular filtration rate (eGFR) using the Schwartz formula, eGFR (Schwartz) = (0.413 x height in cm) / serum creatinine in mg/dL.

Due to lack of data in pediatric patients with an eGFR < 50 mL/min/1.73 m^2 and the risk of increased exposure, avoid use of PRADAXA Oral Pellets in these patients. Treat patients with an eGFR > 50 mL/min/1.73 m^2 with the dosage according to Tables 1 and 2 *[see Dosage and Administration (2.2)]*.

2.4 Administration

PRADAXA Oral Pellets are administered twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

If a dose of PRADAXA Oral Pellets is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA Oral Pellets should not be doubled to make up for a missed dose.

If a partial dose has been taken, a second dose should not be administered at that time. The next dose should be taken as scheduled approximately 12 hours later.

The prepared medication should be given before meals to ensure that the patient takes the full dose.

PRADAXA Oral Pellets should be administered immediately after mixing or within 30 minutes after mixing. If the PRADAXA dose is not administered within 30 minutes of mixing, the dose should be discarded, and a new dose prepared.

PRADAXA Oral Pellets should be administered with only specific soft foods or apple juice.

Administration with soft foods
PRADAXA Oral Pellets may be mixed with two teaspoons of the following soft foods at room temperature:

- Mashed carrots
- Apple sauce
- Mashed banana

Administration with apple juice
PRADAXA Oral Pellets may be spooned directly into the patient's mouth and swallowed with apple juice or added to approximately 1-2 ounces of apple juice for drinking.

PRADAXA Oral Pellets should not be administered:

- via syringes or feeding tubes
- with milk, milk products, or soft foods containing milk products

Instruct patients/caregivers to discard the desiccant once the package is opened.

See **Instructions for Use**.

2.5 Converting from or to Warfarin
When converting patients from warfarin therapy to PRADAXA Oral Pellets, discontinue warfarin and start PRADAXA Oral Pellets when the INR is below 2.0.

When converting from PRADAXA Oral Pellets to warfarin, adjust the starting time of warfarin as follows:

- For eGFR ≥ 50 mL/min/1.73 m^2, start warfarin 3 days before discontinuing PRADAXA Oral Pellets.
- Patients with an eGFR < 50 mL/min/1.73 m^2 have not been studied. Avoid use of PRADAXA Oral Pellets in these patients.

Because PRADAXA Oral Pellets can increase INR, the INR will better reflect warfarin's effect only after PRADAXA Oral Pellets have been stopped for at least 2 days *[see Clinical Pharmacology (12.2)]*.

2.6 Converting from or to Parenteral Anticoagulants
For pediatric patients currently receiving a parenteral anticoagulant, start PRADAXA Oral Pellets 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For pediatric patients currently taking PRADAXA Oral Pellets, wait 12 hours after the last dose before switching to a parenteral anticoagulant *[see Clinical Pharmacology (12.3)]*.

2.7 Discontinuation for Surgery and Other Interventions
If possible, discontinue PRADAXA Oral Pellets before invasive or surgical procedures because of the increased risk of bleeding. For pediatric patients, PRADAXA Oral Pellets should be stopped 24 hours before an elective surgery (eGFR > 80 mL/min/1.73 m^2) or 2 days before an elective surgery (eGFR 50-80 mL/min/1.73 m^2). Pediatric patients with an eGFR < 50 mL/min/1.73 m^2 have not been studied, avoid use of PRADAXA Oral Pellets in these patients.

Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

If surgery cannot be delayed, there is an increased risk of bleeding *[see Warnings and Precautions (5.2)]*. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.1, 5.3)]*. In adults, a specific reversal agent (idarucizumab) is available in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed. Efficacy and safety of idarucizumab have not been established in pediatric patients *[see Warnings and Precautions (5.2)]*. Refer to the idarucizumab prescribing information for additional information. Restart PRADAXA Oral Pellets as soon as medically appropriate.

3 DOSAGE FORMS AND STRENGTHS

PRADAXA Oral Pellets are available in the following strengths:

- 20 mg yellowish pellets in a packet
- 30 mg yellowish pellets in a packet
- 40 mg yellowish pellets in a packet
- 50 mg yellowish pellets in a packet
- 110 mg yellowish pellets in a packet
- 150 mg yellowish pellets in a packet

4 CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- History of a serious hypersensitivity reaction to dabigatran, dabigatran etexilate, or to one of the excipients of the product (e.g., anaphylactic reaction or anaphylactic shock) *[see Adverse Reactions (6.1)]*
- Mechanical prosthetic heart valve *[see Warnings and Precautions (5.4)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation
Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA Oral Pellets are discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant and restart PRADAXA Oral Pellets as soon as medically appropriate *[see Dosage and Administration (2.5, 2.6, 2.7)]*.

5.2 Risk of Bleeding
PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA Oral Pellets in patients with active pathological bleeding *[see Dosage and Administration (2.2)]*.

Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment *[see Clinical Pharmacology (12.2)]*.

Reversal of Anticoagulant Effect
Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited *[see Overdosage (10)]*. Prothrombin complex concentrates or recombinant Factor VIIa may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

In adults, a specific reversal agent (idarucizumab) for PRADAXA is available when reversal of the anticoagulant effect of dabigatran is needed. In pediatric patients, the efficacy and safety of idarucizumab have not been established.

5.3 Spinal/Epidural Anesthesia or Puncture
When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of PRADAXA and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), and bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves
The safety and efficacy of PRADAXA Capsules in adult patients with bileaflet mechanical prosthetic heart valves was evaluated in the RE-ALIGN trial, in which patients with bileaflet mechanical prosthetic heart valves (recently implanted or implanted more than three months prior to enrollment) were randomized to dose-adjusted warfarin or 150 mg, 220 mg, or 300 mg of PRADAXA Capsules twice a day. RE-ALIGN was terminated early due to the occurrence of significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) in the PRADAXA treatment arm as compared to the warfarin treatment arm. These bleeding and thromboembolic events were seen both in patients who were initiated on PRADAXA Capsules postoperatively within three days of mechanical bileaflet valve implantation, as well as in patients whose valves had been implanted more than three months prior to enrollment. Therefore, the use of PRADAXA is contraindicated in all patients with mechanical prosthetic valves *[see Contraindications (4)]*.

The use of PRADAXA for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended.

5.5 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure
The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided *[see Clinical Pharmacology (12.3)]*.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

The concomitant use of PRADAXA Oral Pellets with P-gp-inhibitors has not been studied in pediatric patients but may increase exposure to dabigatran.

5.6 Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome
Direct-acting oral anticoagulants (DOACs), including PRADAXA, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple-positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Risk of Thrombotic Events after Premature Discontinuation *[see Warnings and Precautions (5.1)]*
- Risk of Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions (5.3)]*
- Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves *[see Warnings and Precautions (5.4)]*
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome *[see Warnings and Precautions (5.6)]*

The most serious adverse reactions reported with PRADAXA were related to bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pediatric Trials

Treatment of VTE in Pediatric Patients
The safety of PRADAXA in the treatment of VTE in pediatric patients was studied in one phase III trial (DIVERSITY). The DIVERSITY study was a randomized, open-label, active-controlled, parallel-group trial comparing PRADAXA with standard of care – SOC (vitamin K antagonists, low molecular weight heparin, or fondaparinux). There were 266 pediatric patients who received study treatment, 176 patients treated with PRADAXA and 90 patients treated with SOC. Patients on PRADAXA received age- and weight-adjusted dosages of an age-appropriate formulation of PRADAXA (capsules, pellets, or oral solution) twice daily.

Patients had a median age of 14 years (range: 0-17 years), 92% were white, and half the patients were male (50%). Following at least 5 days of parenteral anticoagulant therapy, the median duration of treatment with PRADAXA was 85 days (range: 1-105). Patients with estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 were excluded from the trial.

Bleeding
Data on adjudicated major bleeding, clinically relevant non-major (CRNM) bleeding, and minor bleeding events for the PRADAXA group and the SOC group in the DIVERSITY study are reported in Table 3. There was no statistically significant difference in the time to first major bleeding event.

Table 3 Summary of All Adjudicated Bleeding Events During On-Treatment Period in DIVERSITY

	PRADAXA N (%)	**Standard of Care (SOC) N (%)**
Patients	**N=176**	**N=90**
Major bleeding event[1]	4 (2.3)	2 (2.2)
Fatal bleeding	0	1 (1.1)
Clinically relevant non-major bleeding	2 (1.1)	1 (1.1)
Minor bleeding	33 (19)	21 (23)
Major and clinically relevant non-major bleeding	6 (3.4)	3 (3.3)
Any bleeding	38 (22)	22 (24)

[1] Major bleeding event if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

Site-specific bleeding rates were comparable between the two arms, with the exception of the rate of any gastrointestinal bleeds (5.7% in PRADAXA arm vs 1.8% in SOC arm).

Gastrointestinal Adverse Reactions
The incidence of gastrointestinal adverse reactions for patients on PRADAXA and SOC was 32% and 12%, respectively, with the following occurring in ≥ 5% of patients taking PRADAXA: dyspepsia (including term gastro-esophageal reflux disease, gastric pH decreased and esophagitis) in 9% (vs 2%), upper abdominal pain in 5% (vs 1%), vomiting in 8% (vs 2%), nausea 5% (vs 4%), and diarrhea 5% (vs 1%).

Reduction in Risk of Recurrence of VTE in Pediatric Patients
The safety of PRADAXA in the reduction in the risk of recurrence of VTE in pediatric patients was studied in one open-label single-arm trial (Study 2). Study 2 enrolled patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study and received PRADAXA until the clinical risk factor resolved, or up to a maximum of 12 months. There were 213 pediatric patients treated with PRADAXA, in a similar fashion as in the DIVERSITY trial.

Patients had a median age of 14 years (range: 0-18 years), 91% were white, and 55% of patients were male. Patients previously enrolled on DIVERSITY accounted for 43% of patients enrolled on Study 2 (29% from PRADAXA arm and 14% from SOC arm). The median duration of treatment with PRADAXA in Study 2 was 42 weeks (range: 0-56 weeks), with 45% of patients completing the 12-month planned duration, 17% stopping due to resolution of VTE risk factors, 12% stopping due to failure to attain target dabigatran concentration and 6% had an adverse event leading to discontinuation.

During the on-treatment period of Study 2, 3 patients (1.4%) had a major bleeding event, 3 patients (1.4%) had a clinically relevant non-major bleeding event, and 44 patients (20%) had a minor bleeding event. The most common drug-related adverse reactions were dyspepsia (5%), epistaxis (3.3%), nausea (3.3%) and menorrhagia (2.8%).

The adverse reaction profile in pediatric patients was generally consistent with that of adult patients.

Hypersensitivity Reactions in Adult PRADAXA Trials
In adult DVT/PE pivotal studies, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in 0.1% of patients receiving PRADAXA Capsules.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Agranulocytosis, neutropenia, thrombocytopenia
Gastrointestinal Disorders: Esophageal ulcer
Immune System Disorders: Angioedema
Renal and Urinary Disorders: Anticoagulant-related nephropathy
Skin and Subcutaneous Tissue Disorders: Alopecia

7 DRUG INTERACTIONS
The concomitant use of PRADAXA with P-gp inhibitors has not been studied in pediatric patients but may increase exposure to dabigatran *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on PRADAXA use in pregnant women are insufficient to determine drug-associated risks for adverse developmental outcomes. There are risks to the mother associated with untreated venous thromboembolism in pregnancy and a risk of hemorrhage in the mother and fetus associated with the use of anticoagulants *(see Clinical Considerations)*. In pregnant rats treated from implantation until weaning, dabigatran increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition at an exposure 2.6 times the human exposure. At a similar exposure, dabigatran decreased the number of implantations when rats were treated prior to mating and up to implantation (gestation Day 6). Dabigatran administered to pregnant rats and rabbits during organogenesis up to exposures 8 and 13 times the human exposure, respectively, did not induce major malformations. However, the incidence of delayed or irregular ossification of fetal skull bones and vertebrae was increased in the rat *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk for thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reaction

Use of anticoagulants, including PRADAXA, may increase the risk of bleeding in the fetus and neonate. Monitor neonates for bleeding *[see Warnings and Precautions (5.2)]*.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. PRADAXA use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider discontinuation or use of shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions (5.2, 5.3)]*.

Data

Animal Data

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at MRHD of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Dabigatran administered to pregnant rats and rabbits during organogenesis up to maternally toxic doses of 200 mg/kg (8 and 13 times the human exposure, respectively, at a MRHD of 300 mg/day based on AUC comparisons) did not induce major malformations, but increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat.

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.2 Lactation

Risk Summary

There are insufficient data to assess the presence of dabigatran in human milk. There are no data on the effects of dabigatran on the breastfed child or on milk production. Dabigatran and/or its metabolites were present in rat milk. Breastfeeding is not recommended during treatment with PRADAXA.

8.3 Females and Males of Reproductive Potential

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including PRADAXA should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use

The safety and effectiveness of PRADAXA Oral Pellets for the treatment and the reduction in risk of recurrence of venous thromboembolism have been established in pediatric patients less than 12 years of age. Use of PRADAXA Oral Pellets for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients. These studies included an open-label, randomized, parallel-group study and an open-label, single-arm safety study *[see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2)]*. Other age-appropriate pediatric formulations of dabigatran etexilate are available for pediatric patients aged 12 years and older for these indications.

Safety and effectiveness of PRADAXA have not been established in pediatric patients with non-valvular atrial fibrillation or those who have undergone hip replacement surgery.

8.5 Geriatric Use

Clinical studies of PRADAXA Oral Pellets did not include patients 65 years of age and older. Information on the use of PRADAXA Capsules in geriatric patients is available in that prescribing information.

8.6 Renal Impairment

PRADAXA has not been studied in pediatric patients with an eGFR < 50 mL/min/1.73 m^2. Reduced renal function could increase exposure. Dosing recommendations cannot be provided for treatment of these patients. Avoid use of PRADAXA in these patients *[see Dosage and Administration (2.3)]*.

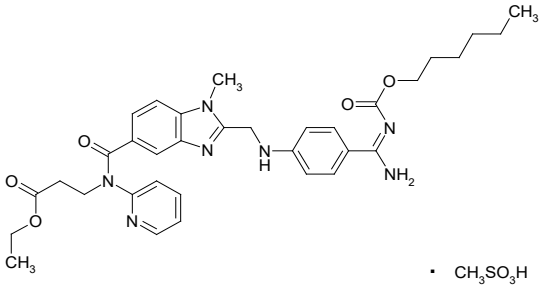
10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. A specific reversal agent (idarucizumab) is available for adult patients.

Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)].*

11 DESCRIPTION

PRADAXA Oral Pellets contain dabigatran etexilate mesylate, a direct thrombin inhibitor. The chemical name of dabigatran etexilate mesylate is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate and it has a molecular formula of $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and molecular weight of 723.86 for the mesylate salt and 627.75 for the free base. The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol. A saturated solution in pure water has a solubility of 1.8 mg/mL.

Each packet of PRADAXA Oral Pellets contains 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, or 150 mg dabigatran etexilate (equivalent to 23.06 mg, 34.59 mg, 46.12 mg, 57.65 mg, 126.83 mg, or 172.95 mg dabigatran etexilate mesylate) along with the following inactive ingredients: acacia, dimethicone, hydroxypropyl cellulose, hypromellose, talc, and tartaric acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, TT, and dTT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring.

As in adults, there is a correlation between plasma dabigatran concentrations and the degree of its anticoagulant effect in pediatric patients with venous thromboembolism. The parameters dTT and ECT increased in direct linear proportion to the plasma concentration of dabigatran, whereas aPTT prolongation increases in a nonlinear fashion with dabigatran plasma concentrations.

Similar PK/PD relationships for aPTT, ECT and dTT were observed across age groups of pediatric patients (ages 26 days to < 18 years) and between pediatric and adult patients with venous thromboembolism. This similarity in PK/PD relationship suggests that similar exposure-response relationship is expected for dabigatran etexilate treatment across the pediatric age groups and adult patients.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy adult subjects and adult patients in the range of doses from 10 mg to 400 mg. Given twice daily, dabigatran's accumulation factor in pediatric patients receiving pellets is 1.5-1.7.

Absorption

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3% to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

PRADAXA is available in Capsules and Oral Pellets. The approved indications and intended age groups are not the same. Oral absorption of dabigatran etexilate is formulation-dependent. Dabigatran etexilate oral pellets show 37% higher relative bioavailability in healthy adults compared to dabigatran etexilate capsules. In addition, the relative bioavailability between the two dosage forms is age dependent. The relative bioavailability observed in adult patients cannot be translated to pediatric patients.

Distribution

Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L.

Elimination

Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The elimination half-life of dabigatran in pediatric patients receiving pellets is approximately 9 to 11 hours.

Metabolism

After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation, forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Specific Populations

Pediatric Patients

The pharmacokinetics of dabigatran was characterized in two clinical studies (DIVERSITY and Study 2) following multiple doses in pediatric patients from birth to less than 18 years old. In pediatric patients taking age- and weight-adjusted dosages of PRADAXA Oral Pellets (less than 12 years of age), the observed geometric mean steady-state trough concentration was 54.7 ng/mL (25.9 to 88.3 ng/mL, 10^{th} to 90^{th} percentile) compared to the geometric mean steady-state trough concentration of 59.7 ng/mL (26.3 to 146 ng/mL, 10^{th} to 90^{th} percentile) observed in adult patients with DVT/PE taking PRADAXA Capsules.

Renal Impairment

An open, parallel-group, single-center study compared dabigatran pharmacokinetics in healthy adult subjects and adult patients with mild to moderate renal impairment receiving a single dose of PRADAXA Capsules 150 mg. Exposure to dabigatran increases with severity of renal function impairment (Table 4). Similar findings were observed in the RE-LY, RE-COVER and RE-NOVATE II trials.

Table 4 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	≥ 80	1x	1x	13
Mild	50-80	1.5x	1.1x	15
Moderate	30-50	3.2x	1.7x	18
Severe[+]	15-30	6.3x	2.1x	27

[+]Patients with severe renal impairment were not studied in RE-LY, RE-COVER and RE-NOVATE II.

Hepatic Impairment

Administration of PRADAXA Capsules in adult patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics.

Drug Interactions

No clinical drug interaction studies have been conducted in pediatric subjects. A summary of the effect of coadministered drugs on dabigatran exposure in adult subjects is shown in Figures 1 and 2.

Figure 1 Effect of P-gp Inhibitor or Inducer (rifampicin) Drugs on Peak and Total Exposure to Dabigatran (C_{max} and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dosage and Dosage Frequency are given as well as the Time of Perpetrator Dosage in Relation to Dabigatran Etexilate Dosage (Time Difference)

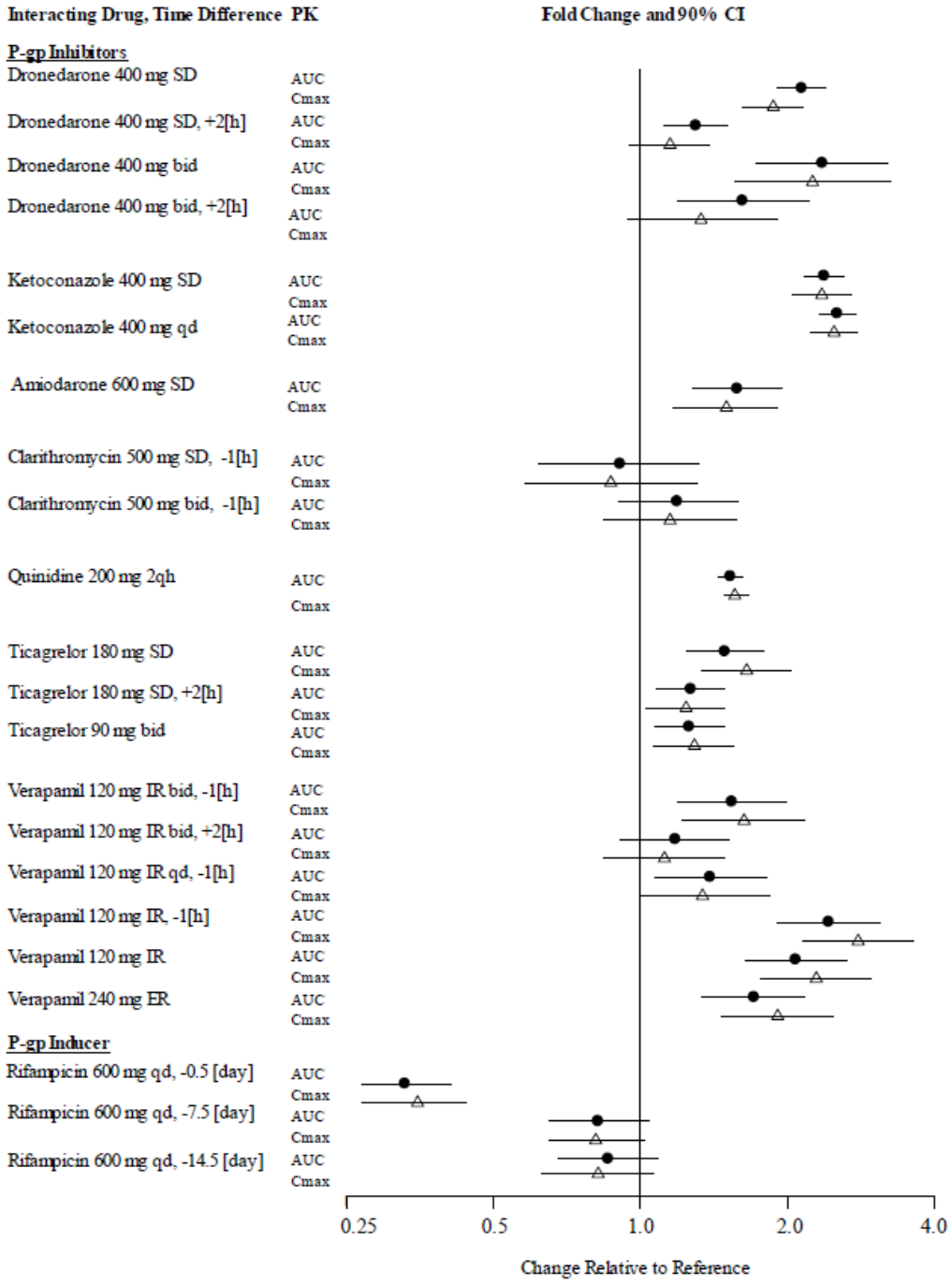
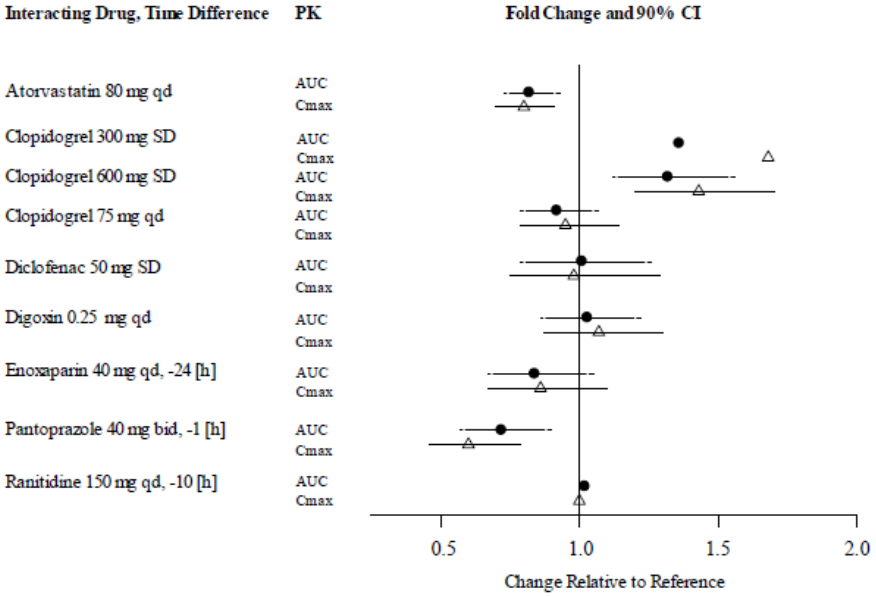


Figure 2 Effect of Non-P-gp Inhibitor or Inducer, Other Drugs, on Peak and Total Exposure to Dabigatran (C_{max} and AUC). Shown are the Geometric Mean Ratios (Ratio) and 90% Confidence Interval (90% CI). The Perpetrator and Dabigatran Etexilate Dosage and Dosage Frequency are given as well as the Time of Perpetrator Dosage in Relation to Dabigatran Etexilate Dosage (Time Difference)



Impact of Dabigatran on Other Drugs
In clinical studies exploring CYP3A4, CYP2C9, P-gp, and other pathways, dabigatran did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Treatment of VTE in Pediatric Patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of PRADAXA compared to standard of care (SOC) for the treatment of venous thromboembolism (VTE) in pediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomized, parallel-group, non-inferiority study. Patients enrolled were randomized according to a 2:1 scheme to either an age-appropriate formulation (capsules, oral pellets, or oral solution) of PRADAXA (dosages adjusted for age and weight) after at least 5 days and no longer than 21 days of treatment with a parenteral anticoagulant, or to SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux. For patients on PRADAXA, drug concentration was determined prior to the 7^{th} dose and a single titration was permitted to achieve drug target levels of 50-250 ng/ml. Inability to achieve target, after one up-titration, resulted in premature termination of study drug in 12 patients (6.8%).

The median treatment duration during the treatment period was 85 days. In total, 267 patients entered the study (leading index VTE was 64% deep vein thrombosis, 10% cerebral venous thrombosis or sinus thrombosis, and 9.0% pulmonary embolism), with 18% of patients having a central line-associated thrombosis. The patient population was 49.8% male, 91.8% white, 4.9% Asian, and 1.5% black; 168 patients were 12 to < 18 years old, 64 patients 2 to < 12 years, and 35 patients were younger than 2 years. The concomitant VTE-related risk factors of patients in this trial among study arms were as follows: inherited thrombophilia disorder (PRADAXA: 20%; SOC: 22%), congenital heart disease (PRADAXA: 12%; SOC: 30%), heart failure (PRADAXA: 3%; SOC: 18%), history of cancer (PRADAXA: 10%; SOC: 1%), CVL insertion (PRADAXA: 23%; SOC: 27%), immobility (PRADAXA: 13%; SOC: 10%) and significant infection (PRADAXA: 15%; SOC: 13%). The number of patients taking concomitant medications with hemostatic effects was similar in both treatment groups (PRADAXA: 15%; SOC: 16%).

The efficacy of PRADAXA was established based on a composite endpoint of patients with complete thrombus resolution, freedom from recurrent venous thromboembolic event, and freedom from mortality related to venous thromboembolic event (composite primary endpoint). Of the 267 randomized patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint. The corresponding rate difference and 95% CI was -0.038 (-0.161, 0.086) and thus demonstrated non-inferiority of PRADAXA to SOC, since the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 20% (see Table 5).

Table 5 Efficacy Results [ITT population] DIVERSITY Study

	PRADAXA	Standard of Care
Number of patients randomized (%)	177 (100.0)	90 (100.0)
Complete thrombus resolution	81 (45.8)	38 (42.2)
Freedom from recurrent VTE	170 (96.0)	83 (92.2)
Freedom from mortality related to VTE	177 (100.0)	89 (98.9)
Composite endpoint met	81 (45.8)	38 (42.2)
Difference in rate (95% CI)[1]	-0.038 (-0.161, 0.086)	
p-value for non-inferiority	< 0.0001	
p-value for superiority	0.2739	

[1] Mantel-Haenszel weighted difference with age group as stratification factor

Subgroup analyses showed that there were no outliers in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors (central venous line, congenital heart disease, malignant disease). For the 3 different age strata, the proportions of patients that met the efficacy endpoint in the PRADAXA and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to < 2 years [Rate Difference -0.052; (95%CI: -0.393, 0.288)], 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to < 12 years [Rate Difference 0.083; (95%CI: -0.176, 0.342)], and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to < 18 years [Rate Difference -0.080; (95%CI: -0.234, 0.074)].

14.2 Reduction in the Risk of Recurrence of VTE in Pediatric Patients

Study 2 was an open-label, single-arm safety study to assess the safety of PRADAXA for the prevention of recurrent VTE in pediatric patients from birth to < 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were included in the study. Eligible patients received age- and weight-adjusted dosages of an age-appropriate formulation (capsules or oral pellets) of PRADAXA until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events, and mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months.

Of the 214 patients in the study, 162 patients were 12 to < 18 years old, 43 patients were 2 to < 12 years old, and 9 patients were aged 6 months to < 2 years old.

The overall probability of being free from recurrence of VTE during the on-treatment period was 0.990 (95% CI: 0.960, 0.997) at 3 months, 0.984 (95% CI: 0.950, 0.995) at 6 months, and 0.984 (95% CI: 0.950, 0.995) at 12 months. The probability of being free from bleeding events during the on-treatment period was 0.849 (95% CI: 0.792, 0.891) at 3 months, 0.785 (95% CI: 0.718, 0.838) at 6 months, and 0.723 (95% CI: 0.645, 0.787) at 12 months. No on-treatment deaths occurred.

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA Oral Pellets are yellowish in a silver-colored, child-resistant packet. The packets are placed in an aluminum bag with a desiccant. PRADAXA Oral Pellets are supplied as follows:

Strength	Package	NDC
20 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0425-78
30 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0430-18
40 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0435-96
50 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0440-53
110 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0445-87
150 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0450-16

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture.

Do not open the packets until ready for use. Use the PRADAXA Oral Pellets within 6 months of opening the aluminum bag containing the packets.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instruction for Use).

Instructions for Patients

- Tell patients or their caregivers to take or administer PRADAXA Oral Pellets exactly as prescribed.
- Tell patients or their caregivers to remove desiccant from the aluminum bag and throw away.
- Remind patients or their caregivers not to discontinue PRADAXA Oral Pellets without talking to the healthcare provider who prescribed it.
- Provide the following instructions on administration to the patients or caregivers:
  - Take the prescribed dosage of PRADAXA Oral Pellets twice a day, approximately 12 hours apart;
  - PRADAXA Oral Pellets may be sprinkled on mashed carrots, apple sauce, or mashed banana, or may be taken with approximately 1-2 ounces of apple juice;
  - PRADAXA Oral Pellets should not be mixed with milk or with foods that contain milk;
  - Once the PRADAXA Oral Pellets are mixed with the soft food or apple juice, the patient should take the dose within 30 minutes;
  - If a dose of PRADAXA Oral Pellets is not taken at the scheduled time, the dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA Oral Pellets should not be doubled to make up for a missed dose.

[see Boxed Warning, and Dosage and Administration (2.2, 2.4)]

Bleeding

Inform patients or their caregivers that they may bleed more easily, may bleed longer, and should call their healthcare provider for any signs or symptoms of bleeding *[see Warnings and Precautions (5.2)]*.

Instruct patients or their caregivers to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients or their caregivers to call their healthcare provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients or their caregivers to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient or their caregivers to contact his or her physician immediately *[see Boxed Warning]*.

Gastrointestinal Adverse Reactions

Instruct patients or their caregivers to call their healthcare provider if they experience any signs or symptoms of dyspepsia or gastritis:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

[see Adverse Reactions (6.1)]

Invasive or Surgical Procedures

Instruct patients or their caregivers to inform their healthcare provider that they are taking PRADAXA before any invasive procedure (including dental procedures) is scheduled *[see Dosage and Administration (2.7)]*.

Concomitant Medications

Ask patients or their caregivers to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the patient's healthcare provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs) or dabigatran exposure (e.g., dronedarone or systemic ketoconazole) *[see Warnings and Precautions (5.2, 5.5)]*.

Prosthetic Heart Valves

Instruct patients or their caregivers to inform their healthcare provider if they will have or have had surgery to place a prosthetic heart valve *[see Warnings and Precautions (5.4)]*.

Allergic Reactions

Advise caregivers that some adults taking PRADAXA have developed symptoms of an allergic reaction. Advise caregivers to inform their child's healthcare provider if their child develops symptoms of an allergic reaction, such as hives, rash, or itching. Advise caregivers to seek emergency medical attention for their child if they develop chest pain or tightness, swelling of the face or tongue, trouble breathing or wheezing, or feeling dizzy or faint.

Pregnancy

Advise patients to inform their healthcare provider immediately if they become pregnant or intend to become pregnant during treatment with PRADAXA *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients not to breastfeed if they are taking PRADAXA *[see Use in Specific Populations (8.2)]*.

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Ridgefield, CT 06877 USA

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COL8834FG192024

MEDICATION GUIDE
PRADAXA (pra dax a)
(dabigatran etexilate)
Oral Pellets

This Medication Guide is for PRADAXA Oral Pellets. If your child is over 8 years of age and your healthcare provider prescribes PRADAXA Capsules for your child, read the Medication Guide that comes with your medicine.

Read this Medication Guide before you start giving PRADAXA Oral Pellets to your child and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your child's medical condition or their treatment.

What is the most important information I should know about PRADAXA?

Do not stop giving PRADAXA without talking to the healthcare provider who prescribes it for your child. Stopping PRADAXA increases your child's risk of a clot forming in their blood.

PRADAXA may need to be stopped, if possible, before surgery or a medical or dental procedure. Ask the healthcare provider who prescribed PRADAXA for your child when your child should stop taking it. Your healthcare provider will tell you when you may start giving PRADAXA to your child again after their surgery or procedure. If your child has to stop taking PRADAXA, your healthcare provider may prescribe another medicine to help prevent a blood clot from forming.

- PRADAXA can cause bleeding which can be serious, and sometimes lead to death. This is because PRADAXA is a blood thinner medicine that lowers the chance of blood clots forming in the body.
- **Your child may have a higher risk of bleeding if your child takes PRADAXA and:**
    - has kidney problems
    - has stomach or intestine bleeding that is recent or keeps coming back, or a stomach ulcer
    - takes other medicines that increase the risk of bleeding, including:
        - aspirin or aspirin-containing products
        - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
        - a medicine that contains warfarin sodium
        - a medicine that contains heparin
        - a medicine that contains clopidogrel bisulfate
        - a medicine that contains prasugrel
    - has certain kidney problems and also takes a medicine that contains dronedarone or ketoconazole tablets

  Tell your healthcare provider if your child takes any of these medicines. Ask your healthcare provider or pharmacist if you are not sure if your child's medicine is one listed above.
- PRADAXA can increase your child's risk of bleeding because it lessens the ability of your child's blood to clot. During treatment with PRADAXA:
    - he or she may bruise more easily
    - it may take longer for any bleeding to stop

  Call your healthcare provider or get medical help right away if your child has any of these signs or symptoms of bleeding:
    - unexpected bleeding or bleeding that lasts a long time, such as:
        - unusual bleeding from the gums
        - nose bleeds that happen often
        - menstrual bleeding or vaginal bleeding that is heavier than normal
    - bleeding that is severe or you cannot control
    - pink or brown urine
    - red or black stools (looks like tar)
    - bruises that happen without a known cause or get larger
    - cough up blood or blood clots
    - vomit blood or your vomit looks like "coffee grounds"
    - unexpected pain, swelling, or joint pain
    - headaches, feeling dizzy or weak

  Take PRADAXA Oral Pellets exactly as prescribed. Do not stop giving PRADAXA Oral Pellets to your child without first talking to the healthcare provider who prescribes it for your child. Stopping PRADAXA increases your child's risk of a clot forming in their blood.
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like PRADAXA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of

forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your child's risk of developing a spinal or epidural blood clot is higher if:

- a thin tube called an epidural catheter is placed in your child's back to give them certain medicine
- your child takes NSAIDs or a medicine to prevent blood from clotting
- your child has a history of difficult or repeated epidural or spinal punctures
- your child has a history of problems with their spine or has had surgery on their spine

If your child takes PRADAXA and receives spinal anesthesia or has a spinal puncture, your healthcare provider should watch your child closely for symptoms of spinal or epidural blood clots. Tell your healthcare provider right away if your child has back pain, tingling, numbness, muscle weakness (especially in the legs and feet), loss of control of the bowels or bladder (incontinence).

See "What are the possible side effects of PRADAXA?" for more information about side effects.

What is PRADAXA Oral Pellets?

PRADAXA Oral Pellets is a prescription medicine that is used to:

- treat blood clots in children who are age 3 months to less than 12 years of age who have received an injectable medicine to treat their blood clots for at least 5 days.
- reduce the risk of blood clots happening again in children who are age 3 months to less than 12 years of age who have already been treated for blood clots.

Do not give PRADAXA if your child:

- currently has certain types of abnormal bleeding. Talk to your healthcare provider before giving PRADAXA if your child currently has unusual bleeding.
- has had a serious allergic reaction to any of the ingredients in PRADAXA. See the end of this Medication Guide for a complete list of ingredients in PRADAXA. Ask your healthcare provider if you are not sure.
- has ever had or if there are plans for your child to have a valve in their heart replaced with a mechanical (artificial) prosthetic heart valve.

Before giving PRADAXA to your child, tell your healthcare provider about all of your child's medical conditions, including if they:

- have kidney problems
- have ever had bleeding problems
- have ever had stomach ulcers
- have antiphospholipid syndrome (APS)
- are pregnant or plan to become pregnant. It is not known if PRADAXA will harm your child's unborn baby.
  - If your child is able to become pregnant, talk with your healthcare provider about your child's risk for severe uterine bleeding during treatment with blood thinner medicines, including PRADAXA.
  - Tell your healthcare provider right away if your child becomes pregnant during treatment with PRADAXA Oral Pellets.
- are breastfeeding or plan to breastfeed. It is not known if PRADAXA passes into your child's breastmilk. Your child should not breastfeed during treatment with PRADAXA.

Tell all of your healthcare providers and dentists that your child is taking PRADAXA. They should talk to the healthcare provider who prescribed PRADAXA for your child before your child has **any** surgery or a medical or dental procedure.

Tell your healthcare provider about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your child's other medicines may affect the way PRADAXA works. Certain medicines may increase your child's risk of bleeding. See **"What is the most important information I should know about PRADAXA?"**

Especially tell your healthcare provider if your child takes a medicine that contains rifampin.

Know the medicines your child takes. Keep a list of them and show it to your healthcare provider and pharmacist when your child gets a new medicine.

How should I give PRADAXA?

- See the detailed **"Instructions for Use"** that comes with PRADAXA Oral Pellets for information about the right way to prepare and give your child a dose of PRADAXA Oral Pellets.
- Your healthcare provider will decide how long your child should take PRADAXA Oral Pellets. **Do not stop giving your child PRADAXA Oral Pellets without first talking with your healthcare provider. Stopping PRADAXA Oral Pellets may increase your child's risk of forming blood clots.**
- **Give PRADAXA Oral Pellets exactly as prescribed by your healthcare provider.** Check with your healthcare provider if you are not sure.
- Your healthcare provider will prescribe the correct dose of PRADAXA Oral Pellets for your child. Your healthcare provider will change your child's dose as they grow, and as needed during treatment.

- Give PRADAXA Oral Pellets 2 times a day, 1 dose in the morning and 1 dose in the evening. The doses should be given as close as possible to every 12 hours, and at about the same time every day.
- Give PRADAXA Oral Pellets before meals to help ensure that your child takes the full dose.
- You can mix PRADAXA Oral Pellets with apple juice or the following soft foods at room temperature:
  - Mashed carrots
  - Apple sauce
  - Mashed bananas
- **Do not** mix PRADAXA Oral Pellets with any food or liquid other than the ones listed above.
- **Do not mix PRADAXA Oral Pellets with milk or with foods that contain milk.**
- Give PRADAXA Oral Pellets right away or within 30 minutes after mixing. **Do not** give PRADAXA Oral Pellets if they have been in contact with the soft food or apple juice for more than 30 minutes.
- **Do not** give PRADAXA Oral Pellets using a syringe or through a feeding tube.
- **Do not** run out of PRADAXA Oral Pellets. Refill your child's prescription before you run out.
- If you plan for your child to have surgery, or a medical or a dental procedure, tell your healthcare provider and dentist that your child is taking PRADAXA Oral Pellets. Your child may have to stop taking PRADAXA Oral Pellets for a short time. See **"What is the most important information I should know about PRADAXA?"**
- If your child only takes part of their dose, **do not** give another dose at that time. Give your child their next dose at the regular scheduled time, about 12 hours later.
- If your child misses a dose of PRADAXA Oral Pellets, give it as soon as you remember. If your child's next dose is less than 6 hours away, skip the missed dose. **Do not** give your child a double dose of PRADAXA Oral Pellets to make up for a missed dose.
- If your child takes too much PRADAXA Oral Pellets, go to the nearest hospital emergency room or call your healthcare provider right away.
- Call your healthcare provider right away if your child falls or injures himself, especially if your child hits his head. Your healthcare provider may need to check your child.

PRADAXA Oral Pellets come in an aluminum bag that contains packets of the Oral Pellets used to prepare your child's dose of medicine. After opening the aluminum bag, the packets of PRADAXA Oral Pellets must be used within 6 months. See **"How should I store PRADAXA Oral Pellets?"**

What are the possible side effects of PRADAXA?

PRADAXA can cause serious side effects. See **"What is the most important information I should know about PRADAXA?"**

- **Allergic Reactions.** Some adults taking PRADAXA Capsules have developed symptoms of an allergic reaction.
  - Call your healthcare provider if your child gets symptoms of an allergic reaction, such as:
    - hives
    - rash
    - itching
  - **Get medical help right away if your child gets any of the following symptoms of a serious allergic reaction with PRADAXA Oral Pellets:**
    - chest pain or chest tightness
    - trouble breathing or wheezing
    - swelling of the face or tongue
    - feeling dizzy or faint

Common side effects of PRADAXA in children include:

- indigestion, upset stomach, burning
- nausea, vomiting, or diarrhea
- stomach-area (abdominal) pain or discomfort

Call your healthcare provider if your child develops any of the signs and symptoms of stomach and intestine problems listed above.

Tell your healthcare provider if your child has any side effect that bothers them or that does not go away.

These are not all of the possible side effects of PRADAXA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PRADAXA Oral Pellets?

- Store PRADAXA Oral Pellets at room temperature 68°F to 77°F (20°C to 25°C).
- After opening the silver aluminum bag that contains the packets of Oral Pellets:
  - The silver aluminum bag contains a desiccant container. Throw away (dispose of) the desiccant container in your household trash.
  - PRADAXA Oral Pellets must be used within 6 months. Safely throw away any unused PRADAXA Oral Pellets after 6 months.
- Keep PRADAXA Oral Pellets packets in the original silver aluminum bag to keep them dry (protect the packets from moisture). **Do not** open packets of PRADAXA Oral Pellets until you are ready to use them.
- Throw away any PRADAXA Oral Pellets that have not been given within 30 minutes after the Oral Pellets come into contact with apple juice or soft food.

Keep PRADAXA and all medicines out of the reach of children.

General information about the safe and effective use of PRADAXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA for a condition for which it was not prescribed. Do not give PRADAXA to other people, even if they have the same symptoms that your child has. It may harm them.

This Medication Guide summarizes the most important information about PRADAXA. If you would like more information, talk with your child's healthcare provider. You can ask your child's pharmacist or healthcare provider for information about PRADAXA that is written for health professionals.

What are the ingredients in PRADAXA Oral Pellets?

Active ingredient: dabigatran etexilate mesylate
Inactive ingredients: acacia, dimethicone, hydroxypropyl cellulose, hypromellose, talc, and tartaric acid.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA

For more information about PRADAXA Oral Pellets, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 6/2025

Instructions for Use
PRADAXA (pra dax a)
(dabigatran etexilate)
Oral Pellets

Read the Medication Guide and this Instructions for Use that come with PRADAXA Oral Pellets for the most important information you need to know before giving PRADAXA Oral Pellets to your child for the first time, and each time you get a refill. The information may have changed. This Instructions for Use does not take the place of talking to your healthcare provider about your child's medical condition or treatment.

Your healthcare provider should tell you the amount (dose) of PRADAXA Oral Pellets to give your child. Your child's dose of PRADAXA Oral Pellets will change as they grow.

Important Information

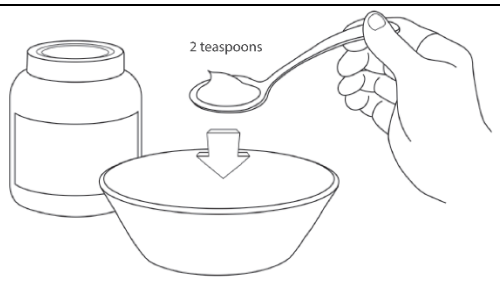
- PRADAXA Oral Pellets can be used in children as soon as they are able to swallow soft food
- **Do not** open the packets of PRADAXA Oral Pellets until you are ready to use them
- Give PRADAXA Oral Pellets either with soft foods or apple juice
- **Do not** give PRADAXA Oral Pellets using syringes or through feeding tubes
- **Do not** mix PRADAXA Oral Pellets with milk or soft foods containing milk products
- Give your child the prepared dose of PRADAXA Oral Pellets before meals to help ensure that your child takes the full dose
- Give PRADAXA Oral Pellets to your child right away or within 30 minutes after mixing
- **Do not** give PRADAXA Oral Pellets if they have been in contact with the food or apple juice for more than 30 minutes
- If your child does not take all of the mixed PRADAXA Oral Pellets, do not give another dose at that time. Give the next scheduled dose about 12 hours later.
- If a dose of PRADAXA Oral Pellets is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA Oral Pellets should not be doubled to make up for a missed dose.

Instructions are provided below for preparing and giving a dose of PRADAXA Oral Pellets with soft foods and preparing and giving a dose of PRADAXA Oral Pellets with apple juice.

How to prepare and give a dose of PRADAXA Oral Pellets with soft foods:
The food should be at room temperature before mixing with the pellets. Use only one of the following soft foods:

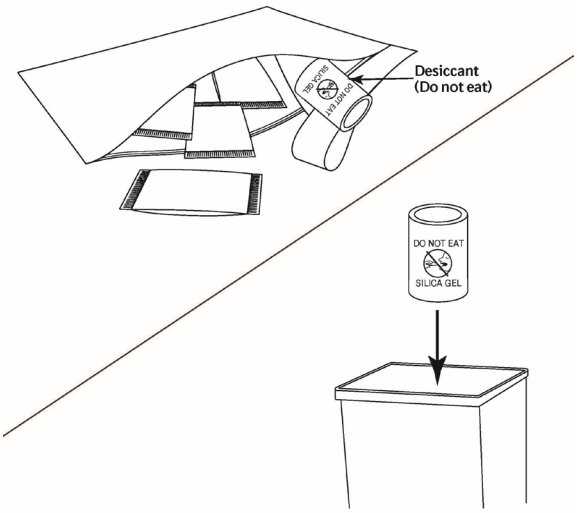
- Mashed carrots
- Apple sauce (for administration with apple juice see below)
- Mashed banana

Do not mix with milk, milk products, or soft foods containing milk products.

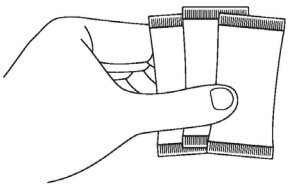
Step 1 – Prepare cup or bowl • Place 2 teaspoons of the soft food into a small cup or bowl.	

Step 2 – Collect PRADAXA Oral Pellets packet(s)

- Open the silver aluminum bag by cutting at the top with scissors. The aluminum bag contains 60 silver-colored packets of PRADAXA Oral Pellets and a desiccant container.
- **Remove desiccant container from silver aluminum bag. Throw away (dispose of) desiccant container in your household trash.**
- **Do not** open or eat the desiccant.

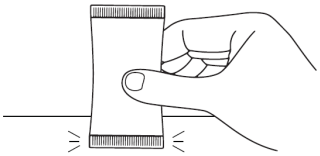


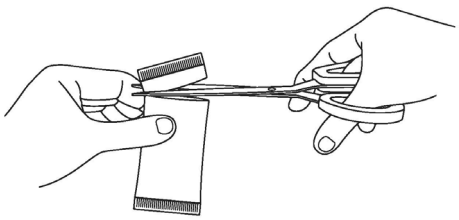
- Remove the prescribed number of PRADAXA Oral Pellets packets from the silver aluminum bag.
- Leave the unused packets of PRADAXA Oral Pellets in the silver aluminum bag.



Step 3 – Open the PRADAXA Oral Pellets packet(s)

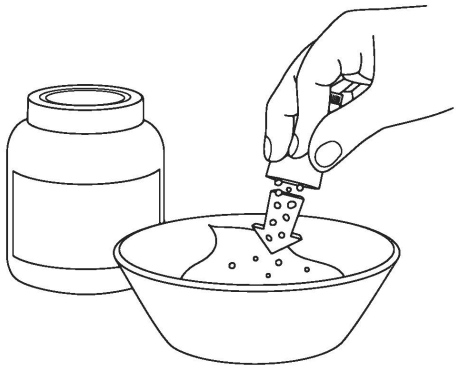
- Tap the packet of Oral Pellets on a flat surface to ensure that the contents settle to the bottom.
- Keep the packet of Oral Pellets in an upright position and open the packet by cutting at the top with scissors.





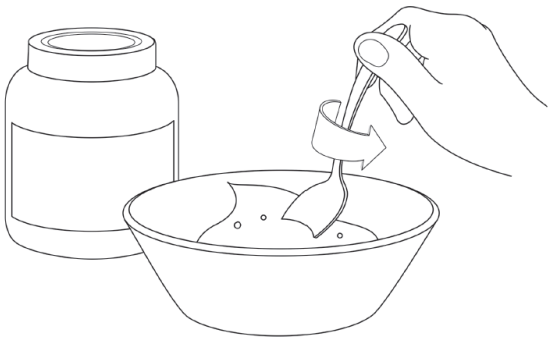
Step 4 – Add the PRADAXA Oral Pellets to soft food

- Empty the entire packet into the small cup or bowl containing the soft food.
- Repeat Steps 3 and 4 if more than one packet is needed.
- Throw away the empty packets in your household trash.



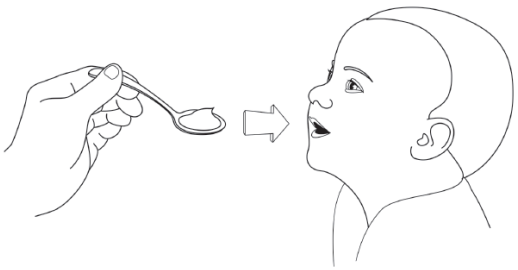
Step 5 – Stir the soft food to mix with the PRADAXA Oral Pellets

- Stir the pellets into the soft food with a spoon to mix well.

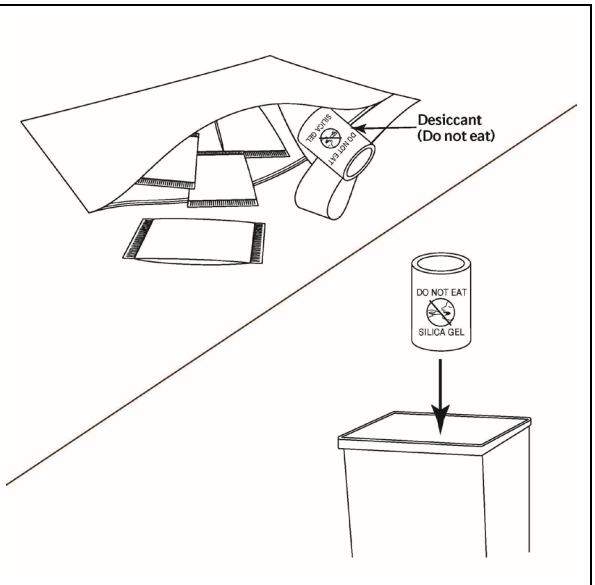
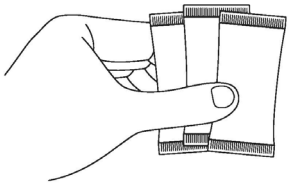


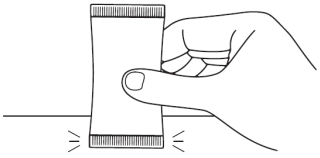
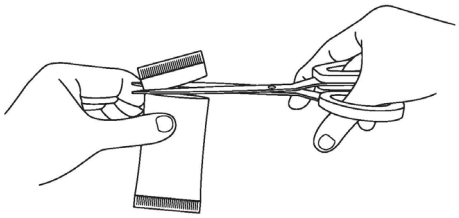
Step 6 – Give the soft food and oral pellet mixture

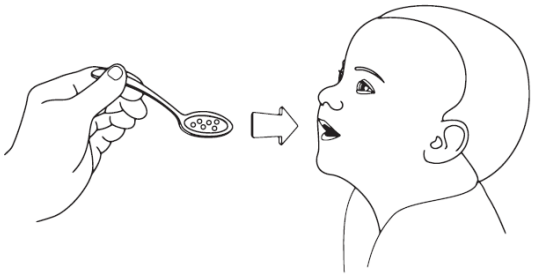
- Give the soft food and oral pellet mixture to your child right away.
- Make sure that your child eats all of the soft food and oral pellet mixture.



How to prepare and give a dose of PRADAXA Oral Pellets with apple juice:

Step 1 – Pour about 1 to 2 ounces of apple juice into a clean drinking cup. **Step 2 – Collect PRADAXA Oral Pellets packet(s)** • Open the silver aluminum bag by cutting at the top with scissors. The silver aluminum bag includes 60 silver-colored packets of pellets and a desiccant container. • **Remove desiccant container from silver aluminum bag. Throw away (dispose of) desiccant container in your household trash.** • **Do not** open or eat the desiccant.	
• Remove the prescribed number of PRADAXA Oral Pellets packets from the silver aluminum bag. • Leave the unused packets of PRADAXA Oral Pellets in the silver aluminum bag.	

Step 3 – Open PRADAXA Oral Pellets packet(s) • Tap the packet on a flat surface to make sure that the contents settle to the bottom. • Keep the packet in an upright position and open the packet by cutting at the top with scissors.	 

Step 4 – Mix the PRADAXA Oral Pellets with apple juice • Spoon the PRADAXA Oral Pellets from the packet into your child's mouth. Offer your child as much apple juice as needed to swallow the PRADAXA Oral Pellets. Make sure all of the PRADAXA Oral Pellets are swallowed. **OR** • Mix the PRADAXA Oral Pellets in a small amount of apple juice that your child is likely to drink completely. Make sure all of the PRADAXA Oral Pellets are swallowed. If any of the PRADAXA Oral Pellets stick to the cup, add a little more apple juice and give it to your child. Repeat until no PRADAXA Oral Pellets remain in the cup.	 

Storing PRADAXA Oral Pellets

- Store PRADAXA Oral Pellets at room temperature from 68°F to 77°F (20°C to 25°C).
- After opening the silver aluminum bag that contains the packets of Oral Pellets:
  - The silver aluminum bag contains a desiccant container. Throw away (dispose of) the desiccant container in your household trash.
  - PRADAXA Oral Pellets must be used within 6 months. Safely throw away any unused PRADAXA Oral Pellets after 6 months.
- Keep PRADAXA Oral Pellets packets in the original silver aluminum bag to keep them dry (protect the packets from moisture). **Do not** open packets of PRADAXA Oral Pellets until you are ready to use them.
- Throw away any PRADAXA Oral Pellets that have not been given within 30 minutes after the Oral Pellets come into contact with apple juice or food.

Keep PRADAXA Oral Pellets and all medicines out of the reach of children.

For more information about PRADAXA Oral Pellets, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA

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Revised: 6/2025

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