Brand Name: Pradaxa®

Generic Name: Dabigatran Etexilate

Manufacturer[1,2]: Boehringer Ingelheim Pharmaceuticals, Inc

Drug Class[1,2]: Anticoagulant, Thrombin Inhibitor

Uses:

- **Labeled uses[1,2]:** reduction in risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- **Unlabeled uses[2]:** postoperative thromboprophylaxis in patients who have undergone total hip or knee replacement procedures, treatment of acute venous thromboembolism

Mechanism of Action[1,2,3,4,7,8]:

- Dabigatran etexilate is a prodrug that is converted to active dabigatran.Dabigatran is a specific, competitive, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. By directly inhibiting thrombin, dabigatran inhibits coagulation by preventing thrombin-mediated effects including cleavage of fibrinogen to fibrin monomers, activation of factors V,VIII, XI, and XIII, and inhibition of thrombin-induced platelet aggregation.

Pharmacokinetics[2,3,4,5,7,8]:

- **Quick reference:**

Parameter	Dabigatran Etexilate
T_{max}	1 hour*
V_d	50-70 liters
$t_{½}$	12-17 hours**
Clearance	80% renally**
Protein Binding	≈ 35%
Bioavailability (F)	3-7%

*****Coadministration with a high fat meal increases Tmax by approximately 2 hours
** In patients with normal renal function

- **Absorption:**
    - Following oral administration, absolute bioavailability was found to be approximately 7%. Dabigatran etexilate is more consistently absorbed in an acidic environment. A dabigatran etexilate coating is applied onto a tartaric acid core to form tiny pellets that are placed in a capsule. In this way, dabigatran etexilate absorption is not dependent on the gastrointestinal acidity of the patient, but

creates its optional pH environment decreasing interpatient and intrapatient variability.

- **Metabolism:**
    - Dabigatran etexilate is cleaved by esterase-catalyzed hydrolysis to the active metabolite dabigatran following oral administration. Dabigatran undergoes hepatic glucuronidation to active acyl glucuronide isomers with similar activity as the parent compound, but these isomers account for less than 10% of total dabigatran in the plasma. Dabigatran is not a substrate, inhibitor, or inducer of any Cytochrome P450 (CYP450) enzyme

- **Elimination:**
    - Dabigatran is eliminated primarily in the urine. Pharmacokinetic changes in impaired renal function are summarized in the table below:

Renal Function	**CrCl (mL/min)**	**Increase in AUC**	**Increase in C_{max}**	**$t_{½}$ (hours)**
Normal	≥ 80	1x	1x	13
Mild	50 – 79	1.5x	1.1x	15
Moderate	31-49	3.2x	1.7x	18

Efficacy[9,10,11]:

- **Connolly SJ, Ezekowitz MD, Yasuf S, Eikelboom J, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY Study). *The New England Journal of Medicine*. 2009 Sept 17; 361(12): 1139-1151.**

  Study Design: phase III, multi-center, prospective, open-label, randomized trial with blinded evaluation of all outcomes

  Description: 18,113 patients with documented atrial fibrillation were recruited from 967 centers in 44 countries. Patients were randomized to receive one of three treatments for 24 months: 110mg dabigatran twice daily (n= 6015), 150mg dabigatran twice daily (n=6076), or adjusted dose warfarin (n=6022. Approximately 50% of randomized patients were naïve to anticoagulation. The primary outcome measure was stroke or systemic embolism. The primary safety outcome measure was major hemorrhage. Stroke or systemic embolism occurred in 182 patients receiving 110mg of dabigatran, 134 patients receiving 150mg dabigatran, and 199 patients receiving warfarin. Both doses of dabigatran were non-inferior to warfarin treatment ($p<0.001$). The 150mg dose of dabigatran was found to be superior to warfarin (relative risk: 0.66, 95% CI: 0.53-0.82; $p<0.001$). The rates of death from any cause were not statistically significant between warfarin and 110mg and 150mg dabigatran groups

(p=0.13 and p=0.51 respectively). The rate of myocardial infarction, however, was higher in both 110mg dabigatran (0.72%) and 150mg dabigatran (0.74%) groups as compared to warfarin (0.53%) (p=0.07 and p=0.048 respectively). As compared to the 110mg dabigatran group, the 150mg dabigatran group and the warfarin group both showed an increased risk of major bleeding (p=0.052 and p=0.003 respectively). Rate of discontinuation at 1 and 2 years were higher in both dabigatran groups than with warfarin (p<0.001). The most common adverse event experienced was dyspepsia which occurred in 11.8% of patients in the 110mg dabigatran group, 11.3% of patients in the 150mg dabigatran group, and 5.8% of patients in the warfarin group (p<0.001).

Limitations: Study participants were permitted to use other anticoagulants during the course of the study. Concomitant use of aspirin by participants was given at baseline, however the use of other anticoagulant medications was not stated at baseline or follow-up/study completion. The use of drugs shown to enhance or hinder the effects of dabigatran was permitted. The funding for the study was provided by Boehringer Ingelheim, which presents a conflict of interest. In the warfarin group, the mean percentage of study period during which the INR was within the therapeutic range was 64%.

Conclusion: As compared to the currently accepted treatment regimen for stroke prevention in atrial fibrillation patients, dabigatran presents an alternative option for treatment. Treatment with 150mg twice daily dabigatran resulted in lower rates of stroke or systemic embolism, lower rates of intracranial bleeding, and higher rates of gastrointestinal bleeding as compared to warfarin. Treatment with dabigatran may be a viable option for patients who are not well controlled with warfarin therapy and who are at a higher risk of intracranial bleeding.

- **Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, et al. Dabigatran With or Without Concomitant Aspirin Compared with Warfarin Alone in Patients with Non-valvular Atrial Fibrillation (PETRO Study).** ***The American Journal of Cardiology*****. 2007 Nov 1; 100(9):1419-1426.**

  Study Design: phase II, multi-center, prospective, double blind, randomized trial

  Description: 502 patients from 53 centers in Denmark, the Netherlands, Sweden, and the United States were randomized to one of 10 treatment groups. Three doses of dabigatran etexilate (50mg twice daily, 150mg twice daily, and 300mg twice daily) were combined with no aspirin, 81mg aspirin, or 325mg aspirin in a 3x3 factorial fashion and compared against warfarin monotherapy. The trial was 12 weeks in duration. The overall purpose of the study was to determine whether there was a dose

related incidence of bleeding. The primary endpoint was incidence of bleeding. Major hemorrhages were observed in the group that received dabigatran 300mg twice daily plus aspirin (three at the 325mg aspirin dose and one at the 81mg aspirin dose). The significantly different incidence rates of major hemorrhage in these groups as compared with the 300mg dabigatran twice daily monotherapy groups ($p<0.02$) led the Safety Monitoring Board to recommend and follow through with alteration of the groups' treatment regimens. The treatments were changed from 300mg dabigatran twice daily plus various aspirin doses to 300mg dabigatran twice daily without aspirin. This decision occurred after patient recruitment and randomization occurred. Total bleeding events were more frequent in the 300mg and 150mg dabigatran groups as compared with the 50mg dabigatran groups ($p=0.0002$ and $p=0.01$ respectively). Conversely, thrombembolic events only occurred in the 50mg dabigatran groups. This trial of several fixed doses of dabigatran with or without aspirin compared to warfarin alone in atrial fibrillation established a dose response for bleeding and an upper limit of tolerability based on the frequency of major and clinically significant bleeding events. It was concluded that dabigatran 150mg twice daily is well tolerated and shows anticoagulant activity and that the upper limit of tolerability for dabigatran is 300mg twice daily plus aspirin.

Limitations: The trial was only 12 weeks in duration. In order to adequately assess the incidence major risks, such as hemorrhage, this trial should have been of longer duration. Although there were no statistically significant differences found between the groups at baseline (all $p>0.05$), the study sample may not adequately reflect the population. The gender stratification of this trial was dramatically weighted toward men, nearly 2/3 of study participants had a documented diagnosis of coronary artery disease, almost ¾ were current or former smokers, and approximately 70% were <75 years of age. These inequalities inhibit the ability to extrapolate the study's results to the entire population of patients with atrial fibrillation. Additionally, Boehringer Ingelheim, the manufacturer of dabigatran etexilate and employer of the study's investigators and committees, funded the study presenting multiple conflicts of interest.

Conclusion: Several important conclusions can be drawn from this study's results. Firstly, the coadministration of dabigatran etexilate with aspirin increases the risk of bleeding. Treatment with 150mg of dabigatran given twice daily provided anticoagulant activity and was well tolerated. Treatment with 50mg of dabigatran given twice daily resulted in higher incidence of systemic thromboembolic events. Adverse events (most commonly gastrointestinal disorders) were more frequent in dabigatran groups than in warfarin treated patients. And finally, the need for further study is established.

- **Schulman S, Kearon C, Kakkar AK, Mismetti P, et al. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER Study). *The New England Journal of Medicine*. 2009 Dec 10; 361(24):2342-2352.**

  Study Design: global, phase III, 6 month, randomized, double-blind, double-dummy, parallel group study

  Description: 2564 patients with acute, symptomatic, objectively verified proximal deep-vein thrombosis from 228 clinical centers in 29 countries were enrolled in the study and randomized to receive a fixed dose of dabigatran (150mg twice daily) or warfarin (adjusted dose to maintain an INR between 2.0 and 3.0) for six months after initial parenteral anticoagulation. A total of 1274 patients were enrolled in the dabigatran group and 1265 patients in the warfarin group. Patients received active dabigatran and placebo warfarin OR active warfarin and placebo dabigatran for the duration of the study. The primary outcome of this study was the incidence of recurrent, symptomatic, objectively confirmed venous thromboembolism (VTE) and related deaths. Safety end points included bleeding events, acute coronary syndromes, other adverse events and liver function tests. Incidence of the primary outcome was confirmed in 30 patients in the dabigatran group and 27 patients in the warfarin group with a difference in risk of 0.4 percentage points (95% confidence interval (CI): -0.8 to 1.5; hazard ratio: 1.10; 95% CI: 0.65 to 1.84). Subsequently, dabigatran treatment was concluded to be noninferior to warfarin therapy with regard to the prevention of recurrent or fatal VTE ($p<0.001$). A total of 20 patients in the dabigatran group and 24 patients in the warfarin group had major bleeding episodes. A total of 71 patients in the dabigatran group as compared with 111 patients in the warfarin group had major or clinically relevant nonmajor bleeding ($p=0.002$). There were 115 patients in the dabigatran group and 86 patients in the warfarin group who had an adverse event that led to discontinuation of the study drug ($p=0.05$). The number of patients who died, had an acute coronary syndrome, or had an elevation in the aspartate aminotransferase level or the alanine aminotransferase level exceeding three times the upper limit of normal while taking the study drug did not differ significantly between the treatment groups. There were no significant differences between the two treatment groups in the frequency of any adverse event except for dyspepsia: 2.9% in the dabigatran group compared to 0.6% in the warfarin group ($p<0.001$).

  Limitations: Approximately 95% of the population was white. Efficacy in other ethnicities was not tested in this study, thus limiting results to those of white ethnicity. With greater than 90% of study participants functioning at a creatinine clearance greater than 50mL/min the efficacy of dabigatran use in patients with renal impairment is not established. Another limitation of the study is the use of parenteral anticoagulants prior to randomization. The use of other anticoagulants limits the applicability of these results to the use of dabigatran after initial anticoagulation with

a parenteral agent; efficacy of monotherapy for VTE prophylaxis was not tested. Finally, Boehringer Ingelheim, the manufacturer of dabigatran, funded the study and employs many of the investigators/authors, thus presenting a conflict of interest.

Conclusion: This study reports dabigatran to be noninferior to warfarin in the prevention of recurrent VTE, however there are still concerns with dabigatran therapy. Firstly, the high rate of patient discontinuation of the drug seen in dabigatran treatment groups creates concern regarding patient compliance and adherence. Secondly, the higher incidence of gastrointestinal adverse events, including dyspepsia, creates apprehension in recommending dabigatran for use in patients with pre-existing gastrointestinal ailments. In contrast, dabigatran therapy resulted in a lower rate of bleeding events (both major and minor) than warfarin therapy. In conclusion, VTE prophylaxis in patients who cannot tolerate warfarin or patients who are at higher risk for bleeding episodes may be candidates for dabigatran therapy.

Contraindications [2,3]: dabigatran etexilate use is contraindicated in patients with:

- Active pathological bleeding
- History of a serious hypersensitivity reaction to dabigatran etexilate

Precautions [1,2,3,6,8]:

- Bleeding: a potential complication of dabigatran etexilate administration is bleeding. Risk factors for bleeding include labor or obstetric delivery and the concurrent use of drugs that increase bleeding risk (anticoagulants, antiplatelet drugs, chronic NSAID use, etc). Dabigatran etexilate use should be discontinued if active pathological bleeding occurs. Patients and practitioners are encouraged to monitor for signs and symptoms of bleeding.
- Dabigatran etexilate should be used in extreme caution in patients undergoing surgery due to increased bleeding risk. Dabigatran etexilate should be discontinued 1-2 days (in patients with CrCl $\geq$ 50mL/min) or 3-5 days (in patients with CrCl < 50mL/min) prior to invasive surgical procedures when possible
    - Consider longer waiting times for patients undergoing major surgery, spinal puncture, placement of a spinal or epidural catheter or port, or in whom complete hemostasis may be required
    - Risk of bleeding should be weighed against the urgency of the surgical intervention. The anticoagulant effect of dabigatran etexilate is best assessed by the ecarin clotting time (ECT). If this test is unavailable, the activated partial thromboplastin time (aPTT) provides an approximation of dabigatran etexilate's anticoagulant activity
- Avoid abrupt discontinuation of dabigatran etexilate as patients who discontinue use prematurely may be at increased risk for stroke

- Use of dabigatran etexilate should be avoided with P-glycoprotein inducers (such as rifampin) as reduction in dabigatran exposure has been seen
- Use of dabigatran etexilate with other anticoagulants (such as other direct thrombin inhibitors, unfractionated heparin or heparin derivatives, low molecular weight heparins, thienopyridines, GPIIb/IIIa antagonists, aspirin, coumarin derivatives, and sulfinpyrazone
- Non-steroidal anti-inflammatory drugs should be used in caution

Adverse effects[1,2,3]:

- Occurrence >10% of patients
    - Gastrointestinal
        - Dyspepsia – including abdominal discomfort pain and epigastric discomfort (11%)
    - Hematologic
        - Bleeding (8% to 33%; major bleeding occurring ≤6%)
- Occurrence 1% to 10%
    - Gastrointestinal
        - GI hemorrhage (≤6%), gastritis-like symptoms (GERD, esophagitis, erosive gastritis, GI ulcer)
    - Hematologic
        - Anemias (1% to 4%), hematoma (1% to 2%), hemoglobin decreased (1% to 2%), hemorrhage (postprocedural or wound: 1% to 2%)
    - Hepatic
        - ALT increased (≥3 times the upper limit of normal: 2% to 3%)
    - Renal
        - Hematuria (1%)
    - Miscellaneous
        - Wound secretion (5%)
        - Postprocedural discharge (1%)
- Occurrence <1%
    - Postmarketing and/or case reports
        - Allergic edema, anaphylactic shock, anaphylaxis, AST increased, blood discharge, ecchymosis, epistaxis, hemarthrosis, hematocrit decreased, hemorrhage (catheter site, hemorrhoidal, incision site, rectal), hepatic function abnormal, intracranial hemorrhage, occult blood positive, pruritus, rash, thrombocytopenia, urticaria

Drug Interactions[2,3,7]:

- P-glycoprotein inhibitors
    - P-glycoprotein inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. However, these results should not

be extrapolated to other P-glycoprotein inhibitors. The use of dabigatran etexilate with P-glycoprotein inhibitors should be avoided.

- P-glycoprotein inducers
  - Rifampin, a P-glycoprotein inducer, decreased dabigatran AUC and C_{max} by 66% and 67% respectively. Concomitant use should be avoided.
- Clopidogrel
  - When given concomitantly with a loading dose of 300mg or 600mg clopidogrel, dabigatran AUC and C_{max} increased 30% and 40% respectively. However, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no change in platelet aggregation inhibition (IPA) as compared to clopidogrel monotherapy. Similarly, coagulation measures for dabigatran's effect (aPTT, ECT, and TT) remained unchanged.
- Pantoprazole
  - Administration of dabigatran etexilate with pantoprazole resulted in a 20% - 30% reduction in dabigatran area under the curve (AUC). No recommendations for dose adjustments have been established.
- Antacids
  - Concomitant administration of antacids with dabigatran etexilate may decrease serum concentrations of dabigatran. No recommendations for dose adjustments have been established.
- Atorvastatin
  - Concomitant administration of atorvastatin with dabigatran etexilate may decrease serum dabigatran concentrations. No recommendations for dose adjustments have been established.
- Herbal products
  - St. John's wort may decrease levels and/or the effects of dabigatran. Concomitant use is not recommended

Dosing/Administration[1,2,3,8]:

- Adult Dosing
  - For stroke prophylaxis and systemic embolism prophylaxis in patients with non-valvular atrial fibrillation
    - 150mg orally twice daily
    - When converting from warfarin to dabigatran etexilate, discontinue warfarin and initiate dabigatran etexilate therapy when INR is <2.0.
    - When converting from a parenteral anticoagulant to dabigatran etexilate, initiate dabigatran etexilate ≤ 2 hours before the time of the next scheduled anticoagulant dose or at the time of discontinuation of a continuously administered anticoagulant
  - For conversion from dabigatran etexilate to warfarin

        - Time to initiation based on renal function
            - CrCl > 50mL/min: start warfarin 3 days before discontinuing dabigatran etexilate
            - CrCl = 31-50mL/min: start warfarin 2 days before discontinuing dabigatran etexilate
            - CrCl = 15-30mL/min: start warfarin 1 day before discontinuing dabigatran etexilate
            - CrCl < 15mL/min: dabigatran etexilate use is contraindicated
        - Dabigatran etexilate can contribute to an elevated INR
            - The INR will be a better indicator of warfarin's effect after dabigatran etexilate administration has been discontinued for at least 2 days
    - For conversion from dabigatran etexilate to a parenteral anticoagulant
        - Discontinue dabigatran etexilate and start the parenteral anticoagulant 12 hours (for patients with CrCl ≥ 30mL/min) or 24 hours (for patients with CrCl < 30mL/min) after the last dabigatran etexilate dose
- Maximum dosage limits
    - Adults: 300mg daily
    - Elderly: 300mg daily
    - Adolescents, Children, Infants, and Neonates : safety and efficacy have not been established
- Dosing for patients with hepatic impairment
    - No specific guidelines are available
- Dosing for patients with renal impairment
    - CrCl > 30mL/min: no dosage adjustment needed
    - CrCl = 15-31mL/min: 75 mg twice daily
    - CrCl < 15mL/min or hemodialysis dependent: use is contraindicated
- Administration
    - Dabigatran etexilate should be taken with water and may be taken with or without food
    - Capsules should be swallowed whole; do not break, chew , or open capsules
    - Missed doses should be administered as soon as possible
        - However, the missed dose should be skipped if it cannot be administered at least 6 hours prior to the next scheduled dose

Storage[3]:

- Capsules should be kept in a tightly closed bottle
- Store between 59°F and 86°F and away from moisture
- Once opened, the product must be used within 30 days

Use in special circumstances:

- **Pregnancy [1,2,3]:**
  - Dabigatran etexilate is a FDA Pregnancy Category C. No adequate, well-controlled studies in pregnant women have been conducted to date
  - Dabigatran etexilate has been shown to decrease the number of implantations when male and female rats were treated with doses of 70mg/kg (about 2.6 to 3.0 times the maximum recommended dose for humans)
  - Treatment of pregnant rats after implantation at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition
- **Lactation [1,2,3]:**
  - It is unknown whether dabigatran is excreted in human milk, therefore caution should be exercised when dabigatran etexilate is administered to a lactating woman
- **Pediatrics [1,3]:**
  - Safety and efficacy of dabigatran etexilate in pediatric patients has not been established
- **Geriatrics [1,2,3]:**
  - No dosage adjustment needed for patients > 65 years of age unless renal impairment exists
  - The risk of stroke and bleeding risk increases with age, but the risk-benefit profile of dabigatran etexilate is favorable for all age groups

Monitoring Parameters[1,2]:

- Serum creatinine
- CBC with differential
- In patients requiring immediate invasive or surgical procedures, the activated partial thromboplastin time (aPTT), ecarin clotting test (ECT), and thrombin time (TT) provide assessment of dabigatran etexilate's anticoagulation activity and the associated bleeding risk

Conclusion:

The use of vitamin K antagonists, such as warfarin, are the mainstay of long-term anticoagulation therapy. However, due to the unpredictable pharmacokinetics, numerous drug, food, and supplement interactions, and the requirement for extensive monitoring, there is a need for newer, safer, effective anticoagulants. While the use of direct thrombin inhibitors, such as dabigatran etexilate, is promising, their indiscriminate use cannot be encouraged at this time. While correcting for many of the deficiencies with vitamin K antagonist use, dabigatran etexilate does have limitations. The incidence of intracranial bleeding is decreased with dabigatran

etexilate use as opposed to warfarin, but the incidence of gastrointestinal bleeding is increased. The high rates of drug discontinuation in dabigatran etexilate treatment groups raise questions of patient adherence. This is compounded by the relatively short half-life of dabigatran etexilate. One missed dose of warfarin may not significantly affect warfarin's efficacy, however one missed dose of dabigatran etexilate may decrease anticoagulant effect putting the patient at risk of stroke, pulmonary embolism, and thrombus formation. This mandates proper patient education regarding vigilant compliance. Other limitations of dabigatran etexilate use include: contraindication in severe renal impairment, unknown pregnancy safety, higher incidence of myocardial infarction seen in some trials, and twice daily dosing. There are, however, some types of patients who may benefit from dabigatran etexilate use: patients whose anticoagulation is unstable with warfarin therapy, those who cannot tolerate the diet restrictions associated with warfarin oral intake, patients at high risk for intracranial bleeding, and patients in whom regular INR monitoring is not an option. When the cost of warfarin acquisition and warfarin monitoring costs are considered, dabigatran etexilate therapy may be more cost effective. This will depend on the price of the brand only Pradaxa® and the frequency of INR monitoring in an individual taking warfarin. The introduction of dabigatran etexilate brings us closer to finding an ideal anticoagulant; however, until full cost analysis and additional studies addressing dabigatran etexilate's limitations are conducted, patients whose anticoagulation is well maintained with warfarin and/or patients who tolerate warfarin well should remain on warfarin therapy. As for other patients, dabigatran etexilate may be a viable option for anticoagulation.

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