

Dabigatran Etxilate

U.S. Fact Sheet

What is Dabigatran Etxilate?

- Dabigatran etexilate is a direct thrombin inhibitor (DTI)¹ in a class of oral anticoagulants being studied for the prevention and treatment of acute and chronic thromboembolic diseases, including:
 - Stroke prevention in patients with non-valvular atrial fibrillation²
 - Prevention of atherothrombotic events in patients with acute coronary syndrome (ACS)³
 - Primary prevention of venous thromboembolism (VTE) in patients undergoing elective total hip or knee replacement surgeries^{4,5,6}
 - Secondary prevention of VTE⁷
 - Treatment of acute VTE⁸

- Dabigatran etexilate is not approved by the FDA for use in the United States. Dabigatran etexilate is approved as Pradaxa® in 40 countries for the primary prevention of venous thromboembolic events (blood clots) in patients who have undergone elective surgery for total hip or total knee replacement.

What is a Direct Thrombin Inhibitor?

- Thrombin is a logical target for anticoagulation because it converts fibrinogen to fibrin, an essential step in thrombus (clot) formation.¹

The Clinical Trial Program for Dabigatran Etxilate - Indications Under Investigation

An extensive clinical trial program is evaluating the efficacy and safety of dabigatran etexilate against current standard therapy in more than 38,000 patients.^{2, 3, 4, 5,6,7,8,9,10} The program includes the RE-LY® (Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared with Dabigatran) study, designed to assess the efficacy of dabigatran etexilate for preventing stroke in patients with non-valvular atrial fibrillation.² The study included 18,113 patients, making it the largest stroke prevention trial in atrial fibrillation to date.²

The following tables summarize the dabigatran etexilate clinical trial program.

Phase II and Phase III Trials in Progress

The following table summarizes Phase II and III studies that are currently underway, or yet to be presented.

Clinical Trial	Study Description	Status
RE-DEEM™ (Phase II)	Dose finding study for dabigatran etexilate in patients with acute coronary syndrome ³	Study ongoing
RE-COVER™ (Phase III)	Efficacy and safety of dabigatran etexilate (150mg twice daily) vs. dose adjusted warfarin (INR = 2.0-3.0) over 6 months of treatment for acute symptomatic VTE ⁸	Study closed
RE-NOVATE® II (Phase III)	Efficacy and safety of dabigatran etexilate (220mg once daily) vs. enoxaparin (40mg subcutaneously once daily) for preventing VTE after surgery for elective total hip arthroplasty ⁶	Study ongoing
RE-MEDY™ (Phase III)	Efficacy and safety of dabigatran etexilate (150mg twice daily) vs. warfarin for secondary prevention of VTE over 18 months ⁷	Recruitment ongoing
RE-SONATE™ (Phase III)	Efficacy and safety of dabigatran etexilate (150mg twice daily) vs. placebo for secondary prevention of VTE over 6 months ⁹	Recruitment ongoing
RE-COVER™ II (Phase III)	Efficacy and safety of dabigatran etexilate (150mg twice daily) vs. warfarin (INR = 2.0-3.0) for 6 month treatment of acute symptomatic VTE ¹¹	Recruitment ongoing
RELY-ABLE™ (Phase III)	Long-term safety of dabigatran etexilate in patients with atrial fibrillation who completed RE-LY® ¹²	Study ongoing
Phase II	Safety and pharmacodynamics of two doses of dabigatran etexilate in addition to standard dual antiplatelet regimen vs. unfractionated heparin in addition to standard dual antiplatelet regimen in patients undergoing elective angioplasty ¹³	Recruitment ongoing
Phase II	Safety and efficacy of dabigatran etexilate in adolescent patients ¹⁴	Recruitment ongoing

Completed Phase III Clinical Trials

The following table summarizes Phase III studies that have been completed to date. Dabigatran etexilate is not approved by the FDA for use in the United States.

Clinical Trial	Study Description	Status
RE-LY® (Phase III)	Efficacy and safety of dabigatran etexilate (110mg or 150mg twice daily) vs. dose adjusted warfarin (international normalized ratio [INR] = 2.0-3.0) for preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation ²	Completed
RE-MODEL™ (Phase III)	Oral dabigatran etexilate (150mg or 220mg once daily) vs. subcutaneous enoxaparin (40mg once daily) for preventing VTE after total knee replacement (European Union, South Africa and Australia) ¹⁰	Completed
RE-NOVATE® (Phase III)	Oral dabigatran etexilate (150mg or 220mg once daily) vs. subcutaneous enoxaparin (40mg once daily) for preventing VTE after total hip replacement (European Union, South Africa and Australia) ⁴	Completed
RE-MOBILIZE® (Phase III)	Oral dabigatran etexilate (150mg or 220mg once daily) vs. subcutaneous enoxaparin (30mg twice daily) for preventing VTE after total knee replacement (North America) ⁵	Completed

For more information about the dabigatran etexilate clinical trial program, please visit www.clinicaltrials.gov.

¹ Di Nisio M, et al. “Direct Thrombin Inhibitors.” *New England Journal of Medicine*. 2005; 353: 1028-40.

² Ezekowitz MD, et al. “Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulation therapy, warfarin, compared with dabigatran.” *American Heart Journal*. 2009; 157: 805-810.

³ ClinicalTrials.gov. “RandomizEd Dabigatran EteXilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-Centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study (RE-DEEM).” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00621855?term=dabigatran&rank=11>. Accessed on: January 28, 2009.

⁴ Eriksson BI, et al. “Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial.” *The Lancet*. 2007; 370:949-956.

⁵ The RE-MOBILIZE Writing Committee. “Oral Thrombin Inhibitor Dabigatran EteXilate vs North American Enoxaprin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty Surgery.” *The Journal of Arthroplasty*. 2009; 24: 1-9

⁶ ClinicalTrials.gov. “A Phase III Randomised, Parallel Group, Double-Blind, Active Controlled Study to Investigate the Efficacy and Safety of Orally Administered 220 mg Dabigatran EteXilate Capsules (110 mg Administered on the Day of Surgery Followed by 220 mg Once Daily) Compared to Subcutaneous 40 mg Enoxaparin Once Daily for 28-35 Days, in Prevention of Venous Thromboembolism in Patients With Primary Elective Total Hip Arthroplasty Surgery. (RE-NOVATE II).” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00657150?term=dabogatran&rank=7>. Accessed on: January 28, 2009.

⁷ ClinicalTrials.gov. “A Randomised, Multicenter, Double-Blind, Active Controlled Study to Investigate the Efficacy and Safety of Dabigatran EteXilate, 150 mg b.i.d Administered Orally (Capsules) for 18 Months, Compared to Warfarin Tablets p.r.n. (Target INR) for the Secondary Prevention of Venous Thromboembolism.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00329238?term=dabigatran&rank=12>. Accessed on: January 28, 2009.

⁸ ClinicalTrials.gov. “A Phase III, Randomised, Double Blind, Parallel-Group Study of the Efficacy and Safety of Oral Dabigatran EteXilate (150 mg Bid) Compared to Warfarin (INR 2.0-3.0) for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism, Following Initial Treatment (5-10 Days) With a Parenteral Anticoagulant Approved for This Indication.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00291330?term=dabigatran+etexilate&rank=11>. Accessed on: August 25, 2009.

⁹ ClinicalTrials.gov. “Twice-Daily Oral Direct Thrombin Inhibitor Dabigatran EteXilate in the Long-Term Prevention of Recurrent Symptomatic Proximal Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00558259?term=dabigatran&rank=1>. Accessed on: April 15, 2009.

¹⁰ Eriksson BI, et al. “Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial.” *Journal of Thrombosis and Haemostasis*. 2007; 5: 2178-2185.

¹¹ ClinicalTrials.gov. “A Phase III, Randomised, Double Blind, Parallel-Group Study of the Efficacy and Safety of Oral Dabigatran Etexilate (150 mg Bid) Compared to Warfarin (INR 2.0-3.0) for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism, Following Initial Treatment (5-10 Days) With a Parenteral Anticoagulant Approved for This Indication.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00680186?term=dabigatran+etexilate&rank=7>. Accessed on: August 25, 2009.

¹² ClinicalTrials.gov. “RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial to Assess the Effect of a Knowledge Translation Intervention on Patients Outcomes.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00808067?term=dabigatran&rank=10>. Accessed on: July 23, 2009.

¹³ ClinicalTrials.gov. “The Safety and Pharmacodynamics of Two Doses of Dabigatran Etexilate in Patients Undergoing Cardiac Catheterization.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00818753?term=dabigatran&rank=7>. Accessed on: July 23, 2009.

¹⁴ ClinicalTrials.gov. “Safety and Tolerability of Dabigatran Etexilate in Adolescents.” Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00844415?term=dabigatran&rank=6>. Accessed on: July 23, 2009.