PRADAXA® (DABIGATRAN ETEXILATE)

Trademark Pradaxa®
(in Japan: Prazaxa®)

EXECUTIVE SUMMARY

- Pradaxa® (dabigatran etexilate) is a non-vitamin K antagonist oral anticoagulant (NOAC) targeting a high unmet medical need in thromboembolic diseases
- Pradaxa® was the first novel breakthrough anticoagulation therapy in over 50 years approved for the prevention of stroke and systemic embolism for adult patients with non-valvular atrial fibrillation (AF) and one or more risk factors for stroke*[1]
- In 2014, Pradaxa® was approved by the European Commission and the US Food and Drug Administration (FDA) for the treatment and prevention of recurrence of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1,2] Since 2008, Pradaxa® has also been approved for the primary prevention of blood clots (venous thromboembolic events) in adults who have undergone elective total hip or total knee replacement surgery[1]
- Clinical experience of Pradaxa® in all licensed indications is already well established and continues to grow, equating to over 6 million patient-years in more than 100 countries worldwide[3]
- Pradaxa® is the only NOAC with more than 6 years' experience in stroke prevention in AF, and long-term data demonstrating the safety and sustained efficacy profile of the treatment in the clinical setting[4,5]
- The safety and efficacy profile of Pradaxa® has been intensely studied during the RE-VOLUTION® clinical trial programme,[4,6–12] as well as evaluated by regulatory authorities in real-world clinical practice[13–15]

*Prior stroke or transient ischaemic attack; age ≥75 years; heart failure (New York Heart Association [NYHA] Class ≥II); diabetes mellitus; hypertension.[1]

Boehringer Ingelheim

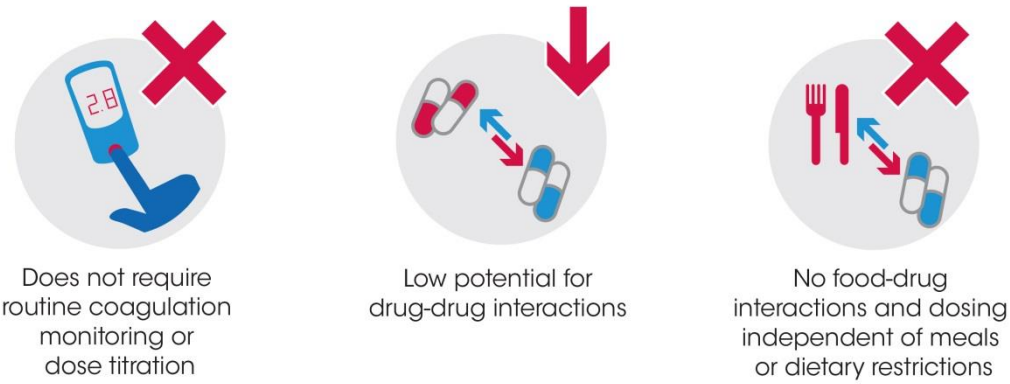
Last updated: August 2016

Profile

Pradaxa® is a novel reversible oral direct thrombin inhibitor that specifically and selectively blocks the activity of thrombin (both free and clot bound), the central enzyme in clot (thrombus) formation.[16,17]

Pradaxa® has a number of characteristics which distinguish it from the long-time standard of care vitamin K antagonist (VKA) therapy e.g. warfarin:

- Does not require routine coagulation monitoring or dose titration[17]
- Predictable and reproducible anticoagulant effect[17]
- Rapid onset/offset of action[17]
- Low potential for drug–drug interactions[17]
- No food–drug interactions and dosing independent of meals or dietary restrictions.[18]



Mode of Action

Unlike other anticoagulants, the effects of direct thrombin inhibitors such as Pradaxa® are targeted specifically to thrombin.[17]

Thrombin is an enzyme in the blood that causes blood to clot by facilitating the conversion of the protein fibrinogen to fibrin. Thrombin clips a small piece off the large protein fibrinogen, converting fibrinogen from a soluble substance into insoluble fibrin, causing it to assemble into large fibrous networks. These networks of fibrin strands then trap blood cells, leading to the formation of blood clots or thrombi, which may ultimately lead to venous thromboembolism and stroke.[16]

Pradaxa® works by specifically and selectively binding to both free and clot-bound thrombin, blocking its activity and effect on blood clotting.[17]

Indications & Approvals

In 2008, the European Commission granted European Union (EU) approval for Pradaxa® for the primary prevention of venous thromboembolic events (blood clots) in adults who have undergone elective total hip or total knee replacement surgery.[1] Following this, in October 2010 Pradaxa® was approved in the US for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors for stroke.*[2] It was then subsequently approved in the EU for this indication in August 2011.[1]

*Prior stroke or transient ischaemic attack; age ≥75 years; heart failure (New York Heart Association [NYHA] Class ≥II); diabetes mellitus; hypertension

In June 2014, Pradaxa® was approved by the European Commission for the treatment and prevention of recurrence of DVT and PE.[1] The US FDA approved Pradaxa® earlier in 2014.[2]

The benefits from Pradaxa® have been widely recognised, leading to regulatory approvals in over 100 countries worldwide. Clinical experience of Pradaxa® is already well established and continues to grow, equating to over 6 million patient-years globally in all licensed indications.[3]

Key Therapeutic Areas under Ongoing Investigation

The safety and efficacy profile of Pradaxa® has been proven within an extensive clinical trial programme, passing independent regulatory approvals worldwide. Boehringer Ingelheim is undertaking ongoing investigation into key areas of unmet need with Pradaxa®. The extensive RE-VOLUTION® clinical trial programme is evaluating the safety and efficacy of Pradaxa® against current standard therapies in major therapeutic areas. Upon completion, the clinical trial programme will involve over 60,000 patients in more than 100 countries globally.[3,4,6–12,19–25]

RE-VOLUTION® Phase III trials	Indication under investigation
RE-NOVATE®[8] & RE-NOVATE® II[9]	Primary prevention of VTE following hip replacement surgery
RE-MODEL™[10]	Primary prevention of VTE following knee replacement surgery
RE-MOBILIZE®[20]	Primary prevention of VTE following knee replacement surgery
RE-LY®[6,7]/RELY-ABLE®[4,5]	Prevention of stroke in patients with non-valvular AF at risk of stroke
RE-COVER®[11] & RE-COVER® II[11]	Treatment of acute VTE
RE-MEDY™[12]	Secondary prevention of VTE
RE-SONATE®[12]	Secondary prevention of VTE

Boehringer Ingelheim has announced plans to initiate further large, global clinical trials and registries of Pradaxa® to evaluate its potential for reducing risk of stroke and other life-threatening events in areas of particular unmet medical need:[3,21–25]

- RE-SPECT ESUS™ will investigate the efficacy and safety of Pradaxa® in patients whose first stroke was embolic of undetermined source (ESUS). Embolic strokes occur when a blood clot forms somewhere in the body and travels through the bloodstream to the brain
- RE-DUAL PCI™ will evaluate the efficacy and safety of Pradaxa® in patients with non-valvular AF who have undergone percutaneous coronary intervention (PCI), also known as angioplasty, with stenting
- RE-CIRCUIT® will investigate the efficacy and safety of uninterrupted anticoagulant treatment with Pradaxa® in patients with AF who undergo ablation. Ablation is a routine, minimally invasive procedure that is conducted to normalise the heart rhythm

Pradaxa® is not approved in any country for patients with ESUS. The new trial announcements contained within this factsheet have not received indication approvals.

- RE-SPECT CVT™ will investigate the safety and efficacy of Pradaxa® in patients with cerebral venous thrombosis (CVT). CVT occurs when a blood clot forms in the brain's veins or venous sinuses, the channels that drain blood from the brain. Although relatively rare, CVT requires immediate medical attention

- RE-COVERY DVT/PE™ will provide real-world data on the use of anticoagulants in acute DVT and PE treatment in real-world clinical practice. The registry will generate further evidence on the safety and efficacy of the two approved doses of Pradaxa® compared to the VKA, warfarin.

The studies began enrolment between 2014 and 2016, and will form part of the extensive RE-VOLUTION® clinical trial programme.

The Global Registry on Long-Term Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA™-AF) will collect important data on the safety and comparative effectiveness of anticoagulant treatments, including warfarin, acetylsalicylic acid (ASA) and NOACs, such as Pradaxa®. Up to 56,000 patients are planned for enrolment across 2,200 sites in 50 countries by 2020, with data being collected from general practices, specialist offices, community hospitals, university hospitals, outpatient care centres and anticoagulation clinics.[26]

Stroke Prevention in Non-Valvular AF

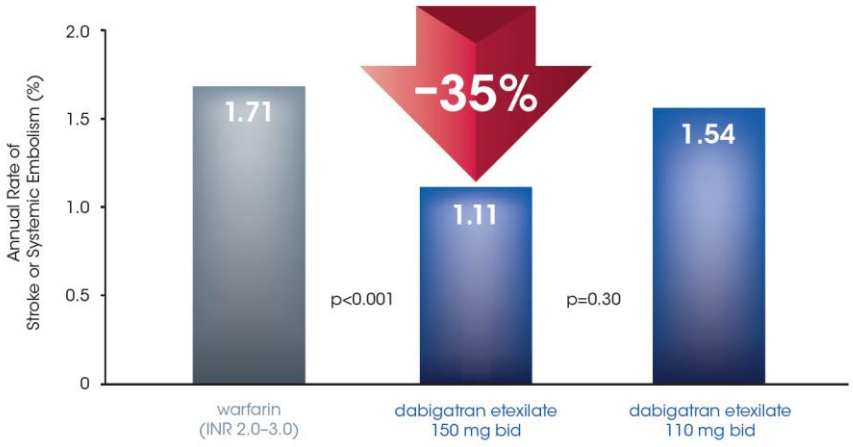
RE-LY® (Randomized Evaluation of Long-term anticoagulant therapY) was a global, Phase III, PROBE (prospective, randomized, open-label with blinded endpoint evaluation) trial of 18,113 patients enrolled in over 951 centres in 44 countries. It was designed to compare two fixed doses of the oral direct thrombin inhibitor Pradaxa® (110 mg and 150 mg twice daily) each administered in a blinded manner, with open label warfarin (INR 2.0–3.0, median TTR 67%[1]).[6,7,27]

Key fact: RE-LY® was one of the largest Phase III trials for stroke prevention in AF, enrolling 18,113 patients in 951 centres in 44 countries. RE-LY® investigated two doses of Pradaxa® in a randomised fashion against well-controlled warfarin.[6]

The RE-LY® trial showed that Pradaxa® 150 mg twice daily was superior to warfarin for stroke prevention in AF[6,7] in an intention-to-treat (ITT) analysis (the ITT analysis represents the highest standard for analysing superiority in non-inferiority trials).[6,7]

Results from RE-LY® demonstrated:[6,7]

- Pradaxa® 150 mg twice daily reduced the risk of stroke and systemic embolism by 35% compared to warfarin

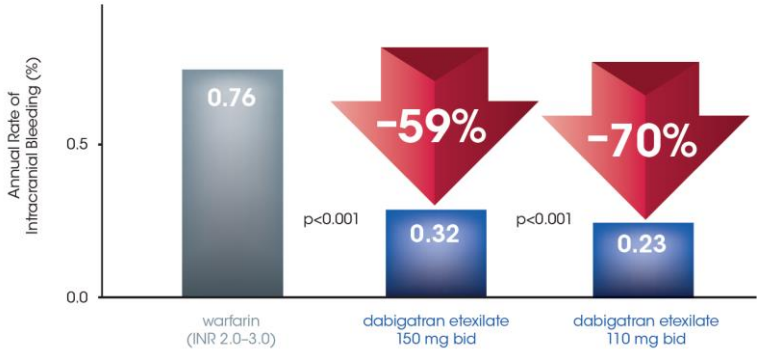


- Pradaxa® 110 mg twice daily showed a similar reduction in the risk of stroke and systemic embolism compared to warfarin.[6,7] Pradaxa® 110 mg twice daily is indicated for certain patients with AF including those aged over 80 years, and those with medical conditions such as decreased renal function or taking concomitant treatments, which put them at higher risk of bleeding.[1]

Pradaxa® 150 mg twice daily is the only non-vitamin K antagonist oral anticoagulant, study of which has shown a significant reduction of both ischaemic and haemorrhagic strokes compared to warfarin in the pivotal RE-LY® trial.[6,7]

In terms of reductions in rates of life-threatening bleeding events and intracranial bleeding, treatment with Pradaxa® was associated with considerable benefit:[6,7]

- Pradaxa® 110 mg twice daily showed lower rates of major bleeding compared to warfarin – the primary safety endpoint of the RE-LY® trial
- Both the 150 mg and 110 mg dose of Pradaxa® showed lower rates of life-threatening and intracranial bleeding than warfarin
- Pradaxa® 150 mg twice daily had similar rates of major bleeding as warfarin - the primary safety endpoint of the RE-LY® trial



- Pradaxa® 150 mg twice daily showed a significant reduction in rates of vascular mortality compared to warfarin.

Following in-depth evaluations of the safety and efficacy of Pradaxa®, regulatory authorities including the European Medicines Agency (EMA) and FDA have reconfirmed the favourable benefit–risk profile of the anticoagulant treatment. The agencies' findings support the substantial benefits that Pradaxa® offers in real-world clinical practice to patients worldwide.[13–15]

Long-term Protection: RELY-ABLE®

Pradaxa® is the first and only NOAC with controlled long-term clinical trial data extending beyond 6 years of ongoing treatment. Results from the RE-LY® follow-up study RELY-ABLE® demonstrate the sustained protection offered by the drug in the clinical setting with good overall long-term safety and tolerability.[4,5]

To ascertain the long-term effects of Pradaxa® in stroke prevention and demonstrate the relative benefits of the two doses available, the RELY-ABLE® (Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) study was undertaken. After completion of the two year RE-LY® trial, patients taking Pradaxa® were followed for a further 2.3 to 4.7 years. The findings demonstrate the long-term protective effects of Pradaxa® in the clinical setting, with benefits sustained beyond 6 years of ongoing treatment with good overall long-term safety and tolerability.[4,5]

The unique results from RELY-ABLE® support the benefits of Pradaxa® beyond six years of long-term treatment:[4,5]

- During the additional follow-up period which extended to 4.7 years of treatment beyond RE-LY®, rates of major events for both Pradaxa® 110 mg and 150 mg twice daily were consistent with those seen in RE-LY®[4,5]
  - Consistent rates of ischaemic and haemorrhagic stroke, and major bleeding, with both doses of Pradaxa® compared to the event rates that occurred during the RE-LY® trial[4,5]
  - The incidence of haemorrhagic stroke was very low and similar between treatment arms[4,5]
  - Very low rates of intracranial bleeding were sustained through the RELY-ABLE® study[4,5]
- There were no new safety findings identified during the additional observation period of RELY-ABLE®.[4,5]

Prevention of Venous Thromboembolism (VTE) in Patients Following Total Knee or Hip Replacement

Results from the RE-NOVATE®, RE-NOVATE II® and RE-MODEL™ trials show that Pradaxa® is as effective as the low-molecular weight heparin, enoxaparin, in preventing VTE after total knee or hip replacement surgery.[8–10] The safety profile of Pradaxa® is comparable to enoxaparin after total knee or hip replacement surgery, with a low incidence of major bleeding events[8–10, 20] and no significant difference was observed in the risk of acute coronary syndrome between treatments.[28]

This evidence from clinical trials is confirmed by experience in the real-world setting. An international observational study with Pradaxa® 220 mg once daily demonstrated that the treatment offered a good safety profile and was associated with a very low overall incidence of bleeding events, including major bleeding events and major extra-surgical bleeding events. With regards to efficacy, the study showed low incidence of VTE and all-cause mortality.[29] These real-world results confirm the benefits of Pradaxa® for the prevention of VTE in patients undergoing total knee or total hip replacement as previously demonstrated in clinical trials.

Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) and Prevention of Recurrence of DVT and PE

The regulatory approvals of Pradaxa® in DVT and PE are based on the results of three global Phase III studies (RE-COVER® / RE-COVER® II / RE-MEDY™) involving almost 10,000 patients. Pradaxa® was demonstrated to be as effective as warfarin with significantly lower rates of bleeding.[11,12] Data from a fourth trial (RE-SONATE®) showed a 92% reduction in the risk of recurrent blood clots versus placebo.[12]

Pradaxa® is a simple and convenient treatment option for DVT and PE patients and their physicians as it does not require routine dose monitoring, nor a mandatory dose change during the course of treatment. DVT and PE patients can start taking Pradaxa® in a simple fixed-dose regimen after initial treatment with an injectable anticoagulant such as low-molecular weight heparin.[1]

Real-world Clinical Practice

The safety profile of Pradaxa® has been intensely studied during the clinical trials programme as well as evaluated by regulatory authorities in real-world clinical practice.[4–15] Both the EMA and FDA have reaffirmed the safety profile and important health benefits of Pradaxa® for patients with non-valvular AF when used as directed.[13–15]

A FDA Drug Safety Communication published on 13 May 2014 included results from a Medicare study of more than 134,000 non-valvular AF patients who were 65 years of age or older and new users of either Pradaxa® or warfarin.[14,15]

The real-world findings from the Medicare study are consistent with the RE-LY® clinical trial results that provided the basis for the approval of Pradaxa®.[14,15] The Medicare study demonstrated that in new users, Pradaxa® was associated with a lower risk of clot-related strokes, bleeding in the brain and death, than warfarin.[14,15] In line with the known results of the RE-LY® trial, the Medicare study found an increased risk of major gastrointestinal bleeding in new users of Pradaxa® compared to warfarin.[14,15] The myocardial infarction risk was similar for the two drugs.[14,15]

In the US, the licensed doses for Pradaxa® are 150 mg twice daily and 75 mg twice daily for the prevention of stroke and systemic embolism in adult patients with non-valvular AF.[2] The dose of 75 mg twice daily is not authorised in Europe for this indication.[1]

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