REVERSING THE ANTICOAGULANT EFFECTS OF DABIGATRAN ETEXILATE (PRADAXA®)

Boehringer Ingelheim

EXECUTIVE SUMMARY

- Anticoagulant treatment is essential to protect patients with atrial fibrillation (AF) against stroke, and to reduce the risk of recurrent blood clots in patients with an initial venous blood clot (deep vein thrombosis or pulmonary embolism).[1–3] A risk of bleeding is a known possible complication of all anticoagulant treatments including warfarin and non-vitamin K antagonist oral anticoagulants (NOACs)[4]

- Dabigatran has shown a favourable benefit-risk profile during its extensive clinical trial programme[5–12] and also in real-world clinical practice.[13–15] Approved by regulatory authorities worldwide, dabigatran is providing benefits to patients in over 100 countries[16]

- Healthcare professionals are equipped with a range of clinical measures to manage bleeding complications during rare emergency situations.[17] These established clinical measures are similar for all anticoagulant treatments, except vitamin K supplementation which can only be given to patients treated with vitamin K antagonists.[18] With dabigatran there is the additional option of removal from the blood system via haemodialysis.[19] The applicable measures for dabigatran are described in the respective countries' approved product labels

- To advance anticoagulation care, Boehringer Ingelheim developed Praxbind®, a specifically targeted reversal agent to dabigatran, for use in rare emergency situations when patients require urgent reversal of its anticlotting effect.[20,21] Phase I data in healthy volunteers as well as in elderly and renally impaired individuals showed that a 5 minute infusion of Praxbind® (>2 g) led to immediate, complete and sustained reversal of dabigatran.[22,23] Interim analyses of Phase III data from the emergency setting demonstrated that a single 5g dose of Praxbind® immediately reversed the anticoagulant effect of dabigatran in all patients evaluated[24-27]

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A new era in anticoagulation offers treatment alternatives

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder and is associated with approximately three million strokes each year.[28–30]

Patients with AF are at increased risk of experiencing blood clots, which may ultimately raise their risk of stroke five-fold.[29,31] However, the risk of AF-related strokes can be reduced with appropriate anticoagulation therapy using vitamin K antagonists (VKAs; such as warfarin) or non-vitamin K antagonist oral anticoagulants (NOACs), such as dabigatran.[1]

Dabigatran is approved in over 100 countries worldwide.[16] Currently approved indications from the European label include:[19]

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Please note that approved indications may differ by country.

All anticoagulation treatments carry a risk of bleeding complications

Anticoagulant treatment is essential to protect patients with AF against stroke, and to reduce the risk of recurrent blood clots in patients with an initial venous blood clot (deep vein thrombosis or pulmonary embolism).[1–3] A risk of bleeding is a known possible complication of all anticoagulant treatments including warfarin and NOACs, such as dabigatran.[4] Although bleeding complications may not be life-threatening, they can cause worry to patients and sometimes require medical or surgical intervention.[32]

According to the European Heart Rhythm Association (EHRA), the benefits for stroke prevention in AF derived through anticoagulation clearly outweigh the risk from major bleeding.[32] However, latest research shows that the impact of bleeding complications, particularly gastrointestinal (GI) bleeding, is an ongoing concern for both healthcare professionals and patients and may lead to under treatment.[33]

It is important to note that anticoagulant therapies must be administered in accordance with the guidance provided within their respective approved product labels. Clinicians should carefully evaluate individual patient risk factors and closely monitor patients, especially those who may be at increased risk of bleeding.[29,31]

Dabigatran has shown a favourable benefit–risk profile during its extensive clinical trial programme:[5–12]

- The landmark RE-LY® clinical trial demonstrated significantly lower rates of life-threatening and intracranial bleeding with both dabigatran 150 mg and 110 mg twice daily and, additionally, significantly lower rates of major and fatal bleeding events with dabigatran 110 mg twice daily[5,6]
    - RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) trial[34]

- Furthermore, a dedicated sub-analysis showed that in RE-LY®, patients had better survival prognosis and spent less time in intensive care following a major bleed with dabigatran than with warfarin[35]
    - The analysis showed that the 30-day mortality (death within one month) related to a major bleeding event was significantly lower with dabigatran than with warfarin in AF patients requiring long-term treatment in the RE-LY® trial[35]
    - In addition, patients treated with dabigatran left the intensive care unit earlier than warfarin-treated patients[35]
- This research shows that applying existing management strategies in case of a major bleed with dabigatran compared to a major bleed with warfarin resulted in better outcomes, even without the availability of a specific reversal agent[35]

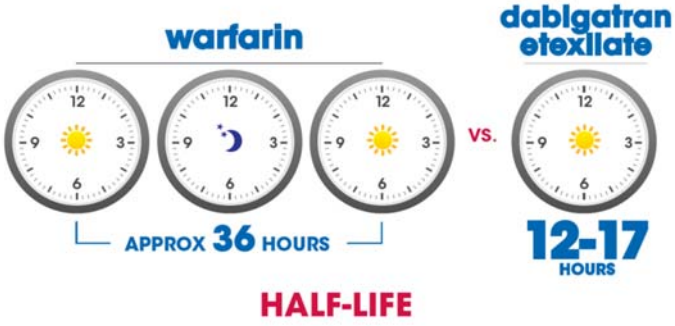
Both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have reaffirmed the safety profile and important health benefits of dabigatran for patients with AF when used as directed.[13–15] The most recent FDA Drug Safety Communication published on 13 May 2014 featured results from an independently conducted Medicare study including real-world data from more than 134,000 AF patients who were 65 years of age or older and new users of either dabigatran or warfarin.[15]

The real-world safety and effectiveness findings from this thoroughly conducted Medicare analysis are consistent with the favourable benefit-risk profile of dabigatran established in the RE-LY® clinical trial.[15] The Medicare study demonstrated that in new users, dabigatran was associated with a lower risk of clot-related strokes, bleeding in the brain and death, than warfarin.[15] In line with the results of the RE-LY® trial, the Medicare study found an increased risk of major gastrointestinal bleeding in new users of dabigatran compared to warfarin.[15] But importantly, the overall risk of major bleeding was equal for patients taking dabigatran and warfarin.[15] The FDA considers dabigatran to have a favourable benefit to risk profile and has explicitly stated that dabigatran “provides an important health benefit when used as directed”.

Please note: In the U.S., the licensed doses of dabigatran for the prevention of stroke and systemic embolism are 150mg twice daily, and 75mg twice daily for certain patient groups.[36] The dose of 75 mg twice daily is not authorised in Europe for this indication.[19]

The half-life of a drug is important when considering reversal

Compared to warfarin, dabigatran has a much shorter half-life (12–17 hours vs. approximately 36 hours for warfarin).[29,31] The anticoagulation effect of dabigatran will therefore clear quicker in the body, potentially simplifying the management of bleeding complications and the antithrombotic regimen during surgery.[31] Because of the short half-life of dabigatran compared to warfarin, in most cases drug discontinuation and standard supportive care is sufficient to manage any anticoagulant-related bleeding complications.[17]



The half-life is the time required for the concentration of a drug to be reduced by one-half of the original concentration. After one half-life period, half of the original drug concentration will have been eliminated and half will remain in the body. After a further half-life time period, half of the remaining drug concentration will be eliminated again and only a quarter of the original will remain. This continues until there is no drug concentration remaining in the body.

Managing bleeding complications

Healthcare professionals are equipped with a range of clinical measures to manage bleeding complications during an emergency situation.[17] Treatment decisions are undertaken upon the basis of the urgency of a situation, location and severity of the bleeding complication and ongoing need for anticoagulation.[37] These established clinical measures are similar for all anticoagulant treatments including warfarin and NOACs, with the exception of vitamin K supplementation, which does not have an effect on the NOACs.[18]

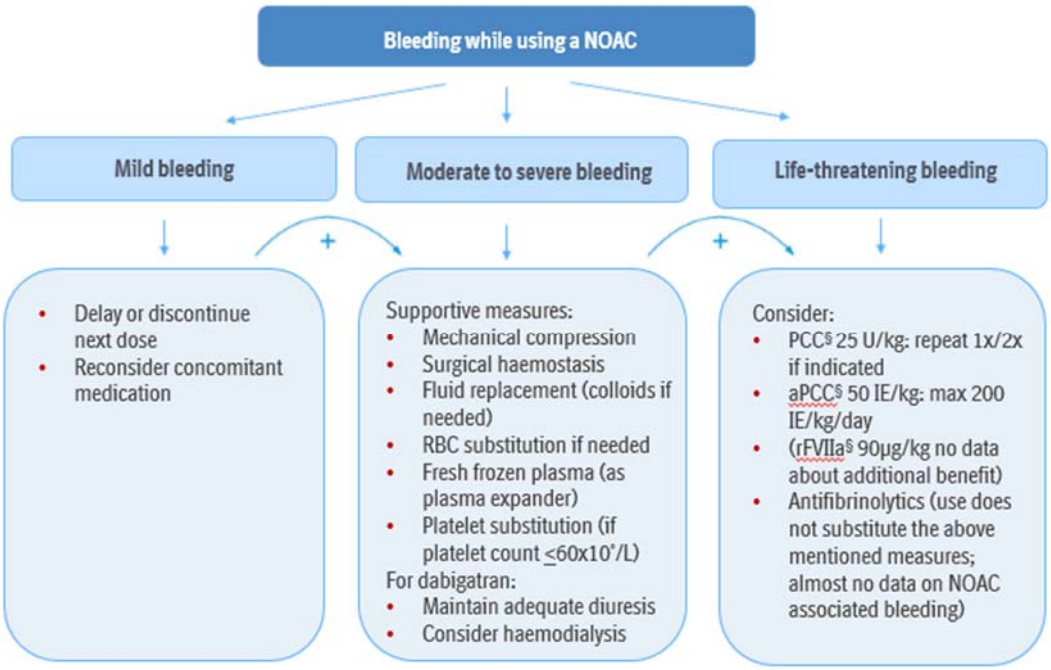
For patients treated with warfarin, therapeutic options for reversing the anticoagulant effect include: [38]

- Vitamin K (phytonadione)
- FFP (fresh frozen plasma)
- Prothrombin complex concentrate (non-activated PCCs or activated PCCs) or recombinant Factor VIIa

Reversal of warfarin is a complex procedure which may take up to 36 hours and could additionally include plasma reconstitution.[38]

For patients treated with NOACs such as dabigatran, a range of options are available to manage bleeding complications.[17,19] In short, the same measures in patients treated with warfarin apply, except vitamin K supplementation.

Management of bleeding complications in patients taking NOACs
European Heart Rhythm Association



§Use in NOAC-associated bleeding based on only very limited experience in humans. Each treating physician should determine what medical treatment and/or bleeding management measures should be taken on a case-by-case basis, based on his/her medical experience and judgement.
Adapted from:
van Ryn J, *et al. Thromb Haemost* 2010;**103**:1116–27.
Heidbuchel H, *et al. Europace* 2013;**15**:625–51.

Activated oral charcoal application (if dabigatran is ingested <2 h before) may also be considered for patients with moderate-to-severe bleeding.[17]*

Dabigatran is the only NOAC that has the additional option of removal from the blood system via haemodialysis, removing about 60% of the dabigatran concentration in 4 hours.[19]

*Recommendation based on limited nonclinical data; for experience in patients, only case studies are available.

Ongoing research to advance anticoagulation care

To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® (idarucizumab), a specifically targeted reversal agent to dabigatran for use in rare emergency situations when patients require urgent reversal of its anticlotting effect.[20,21] The availability of a specific reversal agent has the potential to remove a barrier to anticoagulant treatment, enabling eligible patients who require protection from clot-based strokes caused by AF to receive effective anticoagulation therapy.

In 2015, Praxbind® became the first and only specific reversal agent for a NOAC to be approved by Regulatory Authorities including the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).[39,40] Praxbind® is indicated for adult patients treated with dabigatran who require rapid reversal of its anticoagulant effects prior to urgent procedures / emergency surgery or in life threatening or uncontrolled bleeding.[39,40] Further regulatory reviews are ongoing worldwide and accelerated processes will be pursued with regulatory authorities where available.[16]

Praxbind® binds specifically to dabigatran molecules only, neutralising their anticoagulant effect without interfering with the coagulation cascade.[20,21] This helps physician's focus on other vital aspects of emergency patient management beyond anticoagulant reversal in dabigatran-treated patients.[21]

Phase I studies in healthy volunteers as well as elderly and renally impaired individuals showed that a 5-minute infusion of Praxbind® (>2 g) led to immediate, complete and sustained reversal of dabigatran.[22,23] No clinically relevant side effects were identified and Praxbind® did not over-activate clot production (a pro-coagulant effect).[22,23]

RE-VERSE AD™ is an ongoing, global Phase III patient study initiated by Boehringer Ingelheim in 2014 to investigate Praxbind® in real-world emergency situations.[21,41] The study is designed to reflect the types of patients and real-world situations that physicians would see in the clinical settings requiring emergency interventions.[21] Broad inclusion criteria ensure that even severely ill or injured dabigatran-treated patients (e.g. patients with sepsis, a severe intracranial haemorrhage or a large vessel injury) who require urgent anticoagulant reversal may be enrolled.[21]

Results from a first interim analysis including 90 patients enrolled in RE-VERSE AD™, simultaneously published in the *New England Journal of Medicine (NEJM)* and presented at the International Society of Thrombosis and Haemostasis 2015 Congress in Toronto, Canada in June 2015, demonstrated that:[24,25]

- 5 g of Praxbind® immediately reversed the anticoagulant effect of dabigatran in patients requiring urgent anticoagulant reversal
- After four and 12 hours, laboratory tests showed normal coagulation levels in almost 90 per cent of patients

Updated results from data for 494 patients presented at the American Heart Association (AHA) Scientific Sessions 2016 in New Orleans, Louisiana showed:[27]

- Praxbind® immediately reversed the anticoagulant effect of Pradaxa® in 100 percent of patients
- For patients with extracranial bleeding, median time to confirmation of haemostasis was 3.5 to 4.5 hours, depending on anatomical location
- For patients requiring emergency surgery or an invasive procedure, 93 percent of patients experienced normal haemostasis during surgery, and the median time to the operating room was 1.6 hours after administration of Praxbind®
- No safety signals attributed to Praxbind® were detected. All serious adverse events reported were considered to be related to the index event or comorbidities rather than to study treatment
- Thrombotic events occurred in 6.3 percent (31/494) of patients within 90 days after Praxbind® administration. Approximately two-thirds of these patients received no anticoagulation prior to the event
- Mortality rates at 30 days were 12.3 percent in patients with uncontrolled or life-threatening bleeding and 12.4 percent in patients requiring emergency surgery or an invasive procedure, and 18.7 percent and 18.5 percent at 90 days respectively

Conclusion

A risk of bleeding is a known possible treatment complication with all anticoagulant therapies.[4] A range of established measures to manage bleeding complications are available for use in clinical practice.[17] These measures are almost identical for all anticoagulant treatments, with dabigatran having the additional option of removal from the blood system via haemodialysis.[18,19] To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® as a specific reversal agent to dabigatran.[20,21] Results from clinical trials to date show Praxbind® to be a highly specific reversal agent with a favourable safety profile.[22–27]

References

1. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Syst Rev.* 2005;**3**:CD001927.
2. Marini C, *et al*. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke.* 2005;**36**:1115–9.
3. Dobesh PP, Fanikos J. New Oral Anticoagulants for the Treatment of Venous Thromboembolism: Understanding Differences and Similarities. *Drugs.* 2014;**74**:2015–32.
4. Levine MN, *et al*. Hemorrhagic complications of anticoagulant treatment. *Chest.* 2001;**119**(Suppl.):108S–21S.
5. Connolly SJ, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;**361**:1139–51.
6. Connolly SJ, *et al*. Newly identified events in the RE-LY trial. *N Engl J Med.* 2010;**363**:1875–6.
7. Connolly SJ, *et al*. The Long Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study. *Circulation.* 2013;**128**:237–43.
8. Eriksson BI, *et al*. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet.* 2007;**370**:949–56.
9. Eriksson BI, *et al*. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double blind, non-inferiority trial. *Thromb Haemost.* 2011;**105**:721–9.
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. *Thromb Haemost.* 2007;**5**:2178–85.
11. Schulman S, *et al*. Treatment of Acute Venous Thromboembolism with Dabigatran or Warfarin and Pooled Analysis. *Circulation.* 2014;**129**:764–72.
12. Schulman S, *et al*. Extended use of dabigatran, warfarin or placebo in venous thromboembolism. *N Engl J Med.* 2013;**368**:709–18.
13. European Medicines Agency Press Release, 25 May 2012: EMA/337406/2012. European Medicines Agency updates patient and prescriber information for Pradaxa. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/05/news_detail_001518.jsp&mid=WC0b01ac058004d5c1. Last accessed: November 2016.
14. Graham DJ, *et al.* Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation.* 2015;**131**:157–64.
15. FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin, 13 May 2014. Available at: http://www.fda.gov/drugs/drugsafety/ucm396470.htm. Last accessed: November 2016.
16. Boehringer Ingelheim data on file.
17. van Ryn J, *et al*. Dabigatran etexilate - a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;**103**:1116–27.
18. Kaatz S, *et al.* Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol.* 2012;**87**(Suppl.1):S141–5.
19. Pradaxa® Summary of Product Characteristics, 2016.
20. Schiele F, *et al.* A specific antidote for dabigatran: functional and structural characterization. *Blood.* 2013;**121**:3554–62.
21. Pollack CV, *et al.* Design and rationale for RE-VERSE AD: A phase 3 study of idarucizumab a specific reversal agent for dabigatran. *Thromb Haemost.* 2015;**114**:198–205.
22. Glund S, *et al*. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost.* 2015;**113**:943–51.
23. Glund S, *et al*. Idarucizumab, a Specific Antidote for Dabigatran: Immediate, Complete and Sustained Reversal of Dabigatran Induced Anticoagulation in Elderly and Renally Impaired Subjects. Oral Presentation at The 56th American Society of Hematology Annual Meeting & Exposition, San Francisco, USA, 8 December 2014. *Blood.* 2014;**124**:Abstract 344.
24. Pollack CV, *et al*. Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015;**373**:511–20.
25. Pollack CV Initial results of the RE-VERSE AD trial: idarucizumab reverses the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions. Oral presentation on Monday 22 June 2015 at the International Society of Thrombosis and Haemostasis 2015 Congress, Toronto, Canada.
26. Pollack CV, *et al*. Idarucizumab for Reversal of the Anticoagulant Effects of Dabigatran in Patients in an Emergency Setting of Major Bleeding, Urgent Surgery, or Interventions. 1130M-05. Presented on Saturday 2 April 2016 at the American Congress of Cardiology 65th Annual Scientific Session & Expo, Chicago, USA.
27. Pollack C. V. *et al.* Idarucizumab for Dabigatran Reversal: Updated Results of the RE-VERSE AD Study. Oral presentation on 15 November 2016 at the American Heart Association (AHA) Scientific Sessions 2016, New Orleans, Louisiana, USA
28. Lloyd-Jones DM, *et al*. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042–6.
29. Camm AJ, *et al.* Guidelines for the management of atrial fibrillation. *Eur Heart J.* 2010;**31**:2369–429.
30. Atlas of Heart Disease and Stroke, World Health Organization, September 2004. Available at: http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf. Last accessed: November 2016.
31. Camm AJ, *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J.* 2012;**33**:2719–47.
32. Lip GY, *et al.* Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Thromb Haemost.* 2011;**106**:997–1011.
33. Sarich, *et al*. Novel oral anticoagulants and reversal agents: Considerations for clinical development. *Am Heart J.* 2015;03.010
34. Ezekowitz MD, *et al*. Rationale and design of RE-LY®: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J.* 2009;**157**:805–10.
35. Majeed A, *et al*. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation.* 2013;**128**:2325–32.
36. Pradaxa® US Prescribing Information, 2015.
37. Wiedermann CJ, Stockner I. Warfarin-induced bleeding complications - clinical presentation and therapeutic options. *Thromb Res.* 2008;**122**(Suppl. 2):S13–8.
38. Ansell J, *et al.* Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;**133**(Suppl.):160S–98S.
39. Praxbind® US Prescribing Information, 2015.
40. Praxbind® European Summary of Product Characteristics, 2016.
41. Boehringer Ingelheim Press Release, 22 May 2014. Antidote for rapid reversal of Pradaxa® (dabigatran etexilate) progresses into next stage of clinical investigation with study in patients. Available at https://www.boehringer-ingelheim.com/press-release/antidote-rapid-reversal-pradaxa-dabigatran-etexilate-progresses-next-stage-clinical. Last accessed: November 2016.