# PRAXBIND® – THE SPECIFIC REVERSAL AGENT TO PRADAXA®

To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® (idarucizumab), a specifically targeted reversal agent to Pradaxa® (dabigatran) for use in rare emergency situations when patients require urgent reversal of its anticlotting effect.[1,2] Boehringer Ingelheim began research on Praxbind® in 2009, before the first marketing authorisation of Pradaxa® for stroke prevention in atrial fibrillation (AF) in 2010.[3,4]

In 2015, Praxbind® became the first and only specific reversal agent for a non-vitamin K antagonist oral anticoagulant (NOAC) to be approved by regulatory authorities including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).[5,6] Praxbind® is indicated for adult patients treated with Pradaxa® who require rapid reversal of its anticoagulant effects prior to urgent procedures / emergency surgery or in life-threatening or uncontrolled bleeding.[5,6]

## About Praxbind®

Praxbind® is a humanized antibody fragment (Fab) designed as a specific reversal agent to Pradaxa®.[1]

Praxbind® binds specifically to dabigatran molecules only, neutralising their anticoagulant effect without interfering with the coagulation cascade.[1,2] This helps physicians focus on other vital aspects of emergency patient management beyond anticoagulant reversal in Pradaxa®-treated patients.

## Intended usage

Praxbind® is designed for use in Pradaxa®-treated patients who require urgent anticoagulant reversal:

- Patients requiring urgent procedures / emergency surgery (e.g. surgery for an open fracture after a fall)
- Patients with life-threatening or uncontrolled bleeding complications (e.g. intracranial haemorrhage or severe trauma after a car accident).[2]

## Regulatory milestones

Praxbind® is currently the only specific reversal agent for a NOAC to be approved in the US and the EU.[5,6]

- **February and March 2015:** Praxbind® was submitted under an accelerated approval pathway to the US FDA, EMA and Health Canada for use in Pradaxa®-treated patients who require urgent anticoagulant reversal[7]
- **June 2014** and **May 2015** respectively: The FDA granted Praxbind® both Breakthrough Therapy and Orphan Drug Designation[8,9]
- **October 2015:** The FDA approved Praxbind® for adult patients treated with Pradaxa® who require rapid reversal of its anticoagulant effects prior to emergency surgery / urgent procedures or in life-threatening or uncontrolled bleeding[5]
- **November 2015:** Praxbind® approved in the EU for adult patients treated with Pradaxa® who require rapid reversal of its anticoagulant effects prior to urgent procedures / emergency surgery or in life-threatening or uncontrolled bleeding[6]
- **Future:** Further regulatory reviews around the world are ongoing and accelerated processes will be pursued with regulatory authorities where available[3]

## Efficacy & safety results from Phase I studies

Phase I studies in healthy volunteers have shown:

- A 5 minute infusion of Praxbind® (>2 g) led to immediate, complete and sustained reversal of Pradaxa® (NCT01688830)[10]
- No clinically relevant side effects were identified and Praxbind® did not over activate clot production (a pro-coagulant effect)[10]
- Consistent results have also been seen with the dose of 5 g Praxbind® in elderly and renally-impaired individuals (NCT01955720)[11]
- Praxbind® restored wound-site formation of fibrin, the main component of a blood clot, indicating that Praxbind® both reverses Pradaxa® as well as simultaneously restores coagulation[12]
- Additionally, Pradaxa® treatment could be re-initiated as early as 24 hours after administration of Praxbind® and its anticoagulant effect was restored.[11]

**Phase III study: RE-VERSE AD™ (NCT02104947)**

The efficacy and safety of Praxbind® is now being evaluated in RE-VERSE AD™, an ongoing, global Phase III patient study in the emergency setting (NCT02104947). This study involves Pradaxa® -treated patients who require an urgent procedure / emergency surgery, or experience life-threatening or uncontrolled bleeding complications.[2]

RE-VERSE AD™ is designed to evaluate the types of patients and real-world situations that healthcare professionals may see in the emergency setting. This includes severely ill or injured patients (e.g., patients in an automobile accident with multiple injuries, patients with aortic aneurysm, patients receiving an organ transplant) who as such require urgent reversal of dabigatran.[2] Up to 500 Pradaxa®-treated patients aged 18 years or over are expected to be enrolled from more than 400 centres in more than 35 countries worldwide.[2,13,14]

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:[15,16]

- 5 g of Praxbind® immediately reversed the anticoagulant effect of Pradaxa® in patients requiring urgent anticoagulant reversal
- After 4 and 12 hours, laboratory tests showed normal coagulation levels in almost 90% of patients.

Updated results from data for 494 patients presented at the American Heart Association (AHA) Scientific Sessions 2016 in New Orleans, Louisiana showed:[17]

- 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

## References


1. Schiele F, *et al.* A specific antidote for dabigatran: functional and structural characterization. *Blood.* 2013;**121**:3554–62.
2. 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.
3. Boehringer Ingelheim. Data on File.
4. Pradaxa®. US Prescribing Information, 2015.
5. Praxbind®. US Prescribing Information, 2015.
6. Praxbind®. European Summary of Product Characteristics, 2015.
7. Boehringer Ingelheim Press Release, 3 March 2015. Boehringer Ingelheim submits applications for approval of idarucizumab, specific reversal agent to dabigatran etexilate (Pradaxa®), to EMA, FDA and Health Canada. Available at: https://www.boehringer-ingelheim.com/press-release/boehringer-ingelheim-submits-applications-approval-idarucizumab-specific-reversal. Last accessed: November 2016.
8. Boehringer Ingelheim Press Release, 30 June 2014. U.S. FDA grants Breakthrough Therapy Designation to Pradaxa® (dabigatran etexilate) specific investigational antidote. Available at: https://www.boehringer-ingelheim.com/press-release/us-fda-grants-breakthrough-therapy-designation-pradaxa-dabigatran-etexilate-specific. Last accessed: November 2016.
9. US Food and Drug Administration Orphan Drug Designations and Approvals. Available at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm. Last accessed: November 2016.
10. 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.
11. 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.
12. van Ryn J, *et al*. Effect of Dabigatran on the Ability to Generate Fibrin at a Wound site and its Reversal by Idarucizumab, the Antidote to Dabigatran, in Healthy Volunteers: An Exploratory Marker of Blood Loss. Presented on 18 November 2014 at the American Heart Association Scientific Sessions, Chicago, USA. Available at: http://www.abstractsonline.com/pp8/#!/3547/presentation/33249. Last accessed: November 2016
13. Pollack CV, *et al*. A Phase III Clinical Trial to Evaluate the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD™). Poster presentation at the International Stroke Conference, Nashville, USA, 11-13 February 2015.
14. 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.
15. Pollack CV, *et al*. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;**373**:511–20.
16. 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.
17. 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.