PRAXBIND® – THE SPECIFIC REVERSAL AGENT TO DABIGATRAN

To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® (idarucizumab), a specifically targeted reversal agent to dabigatran etexilate (Pradaxa®) 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 dabigatran for stroke prevention in atrial fibrillation in 2010.[3,4]

Praxbind® is now approved in the European Union (EU) for adult patients treated with dabigatran who require rapid reversal of its anticoagulant effects prior to emergency surgery / urgent procedures or in life threatening or uncontrolled bleeding.[5] The EU approval follows the U.S. Food and Drug Administration (FDA) approval of Praxbind® earlier this year (October 2015).[6] Praxbind® is the first and only specific reversal agent for a non-vitamin K antagonist oral anticoagulant (NOAC) to receive EU and U.S. approval.

About Praxbind®

Praxbind® is a humanized antibody fragment (Fab) designed as a specific reversal agent to dabigatran.[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 dabigatran-treated patients.

Intended usage

Praxbind® is designed for use in dabigatran-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]

- **In February and March 2015** Praxbind® was submitted under an accelerated approval pathway to the U.S. Food and Drug Administration, European Medicines Agency and Health Canada for use in dabigatran-treated patients who require urgent anticoagulant reversal.[7]
- The FDA granted Praxbind® both Breakthrough Therapy and Orphan Drug Designation in **June 2014** and **May 2015** respectively.[8,9]
- In **September 2015** The Committee for Medicinal Products for Human use (CHMP) of the European Medicines Agency (EMA) granted Praxbind® a positive opinion recommending European approval.[10]
- 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 in **October 2015**.[6]
- Praxbind® is **now approved in the European Union** for adult patients treated with dabigatran etexilate who require rapid reversal of its anticoagulant effects prior to urgent procedures / emergency surgery or in life threatening or uncontrolled bleeding.[5]
- Boehringer Ingelheim plans to submit Praxbind® in all countries where dabigatran is licensed. Further submissions 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 dabigatran (NCT01688830)[11]
- No clinically relevant side effects were identified and Praxbind® did not over activate clot production (a pro-coagulant effect)[11]
- Consistent results have also been seen with the dose of 5 g Praxbind® in elderly and renally-impaired individuals (NCT01955720)[12]
- Praxbind® restored wound-site formation of fibrin, the main component of a blood clot, indicating that Praxbind® both reverses dabigatran as well as simultaneously restores coagulation[13]
- Additionally, dabigatran treatment could be re-initiated as early as 24 hours after administration of Praxbind® and its anticoagulant effect was restored.[12]

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 dabigatran-treated patients who require emergency surgery or an urgent procedure, or experience life threatening or uncontrolled bleeding complications.[2]

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

RE-VERSE AD™ is designed to evaluate the types of patients and real-world situations that healthcare professionals may see in the emergency setting. Up to 450 dabigatran-treated patients aged 18 years or over are expected to be enrolled from more than 400 centres in 38 countries worldwide.[2,14]

Results from an interim analysis, 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 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

Further results from the interim analysis were also presented at the ESC Congress 2015 in London, UK in September 2015 and demonstrated that:[17]

- 5 g of Praxbind® enabled emergency surgery to be initiated rapidly in urgent situations involving patients treated with dabigatran

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