

# REVERSING THE ANTICOAGULANT EFFECTS OF DABIGATRAN ETEXILATE (PRADAXA®)

## 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).<sup>1-3</sup> A risk of bleeding is a known possible complication of all anticoagulant treatments including warfarin and non-vitamin K antagonist oral anticoagulants (NOACs)<sup>4</sup>
- Even in the absence of a specific reversal agent, dabigatran has shown a favourable benefit-risk profile during its extensive clinical trial programme<sup>5-12</sup> and also in real-world clinical practice.<sup>13-15</sup> Approved by regulatory authorities worldwide, dabigatran is providing benefits to patients in over 100 countries<sup>16</sup>
- Healthcare professionals are equipped with a range of clinical measures to manage bleeding complications during rare emergency situations.<sup>17</sup> 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.<sup>18</sup> With dabigatran there is the additional option of removal from the blood system via haemodialysis.<sup>19</sup> 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.<sup>20,21</sup> 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.<sup>22,23</sup> An interim analysis of Phase III data from the emergency setting demonstrated that 5 g of Praxbind® immediately reversed the anticoagulant effect of dabigatran in patients requiring urgent anticoagulant reversal<sup>24,25</sup>

## 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.<sup>26–28</sup>



Patients with AF are at increased risk of experiencing blood clots, which may ultimately raise their risk of stroke five-fold.<sup>29</sup> 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.<sup>1</sup>

Dabigatran is approved in over 100 countries worldwide.<sup>16</sup> Currently approved indications from the European label include:<sup>19</sup>

- 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  $\geq 75$  years; heart failure (NYHA Class  $\geq$  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).<sup>1–3</sup> A risk of bleeding is a known possible complication of all anticoagulant treatments including warfarin and NOACs, such as dabigatran.<sup>4</sup> Although bleeding complications may not be life-threatening, they can cause worry to patients and sometimes require medical or surgical intervention.<sup>30</sup>

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.<sup>30</sup> 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.<sup>31</sup>

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.<sup>27,29</sup>

In the absence of a specific reversal agent, dabigatran has shown a favourable benefit–risk profile during its extensive clinical trial programme:<sup>5–12</sup>

- The landmark RE-LY<sup>®</sup> 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<sup>6–7</sup>
  - RE-LY<sup>®</sup> was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) trial.<sup>32</sup>

- 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<sup>33</sup>
  - 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<sup>33</sup>
  - In addition, patients treated with dabigatran left the intensive care unit earlier than warfarin-treated patients<sup>33</sup>
- 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<sup>33</sup>

Both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have reaffirmed the important health benefits and safety profile of dabigatran for patients with AF when used as directed.<sup>13-15</sup>

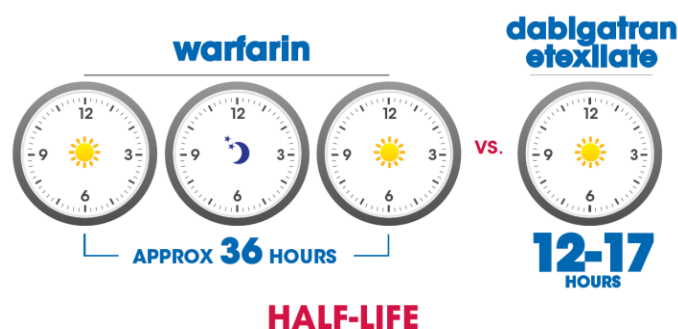
The most recent FDA Drug Safety Communication published on 13 May 2014 included results from a Medicare study of more than 134,000 AF patients who were 65 years of age or older and new users of either dabigatran or warfarin.<sup>15</sup>

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 dabigatran.<sup>15</sup> 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.<sup>15</sup> 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.<sup>15</sup> The risk of myocardial infarction was similar for the two drugs.<sup>15</sup>

*In the United States, the licensed doses for dabigatran 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.<sup>34</sup> The dose of 75 mg twice daily is not authorised in Europe for this indication.<sup>19</sup>*

## 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).<sup>29</sup> 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.<sup>30</sup> 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.<sup>17</sup>



*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

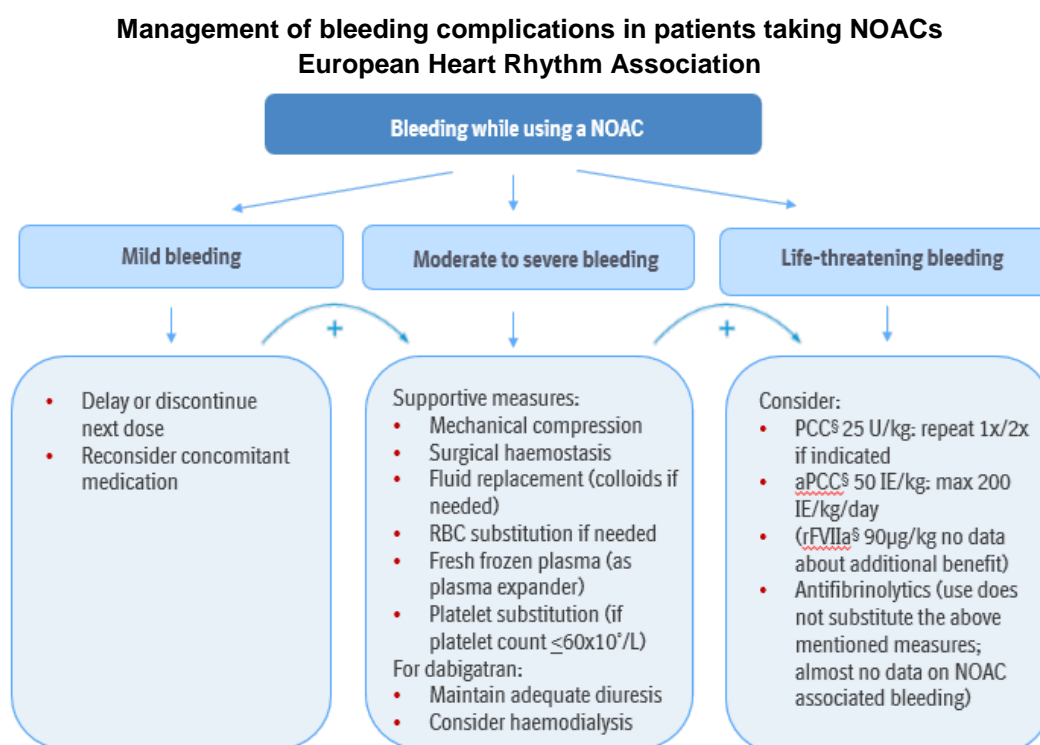
Healthcare professionals are equipped with a range of clinical measures to manage bleeding complications during an emergency situation.<sup>17</sup> Treatment decisions are undertaken upon the basis of the urgency of a situation, location and severity of the bleeding complication and ongoing need for anticoagulation.<sup>35</sup> 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.<sup>18</sup>

For patients treated with warfarin, therapeutic options for reversing the anticoagulant effect include:<sup>36</sup>

- 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.<sup>36</sup>

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



<sup>§</sup>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.<sup>17\*</sup>

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.<sup>19</sup>

\*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.<sup>21</sup> 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.

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.<sup>37</sup> The EU approval follows the FDA approval of Praxbind® earlier this year (October 2015).<sup>38</sup> Praxbind® is the first and only specific reversal agent for a non-vitamin K antagonist oral anticoagulant (NOAC) to receive EU and US approval.

Boehringer Ingelheim plans to submit Praxbind® in all countries where dabigatran is licensed.<sup>16</sup> Further regulatory submissions are ongoing and accelerated processes will be pursued with regulatory authorities where available.<sup>16</sup>

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

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.<sup>22,23</sup> No clinically relevant side effects were identified and Praxbind® did not over-activate clot production (a pro-coagulant effect).<sup>22,23</sup>

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.<sup>21,39</sup> 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.<sup>21</sup> 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.<sup>21</sup>

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:<sup>24,25</sup>

- 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:<sup>40</sup>

- 5 g of Praxbind® enabled emergency surgery to be initiated rapidly in urgent situations involving patients treated with dabigatran
- The median time between administration and surgery was only 1.7 hours and there were no post-surgical bleeding complications reported in the 24 hours following surgery.

## Conclusion

A risk of bleeding is a known possible treatment complication with all anticoagulant therapies.<sup>4</sup> A range of established measures to manage bleeding complications are available for use in clinical practice.<sup>17</sup> These measures are almost identical for all anticoagulant treatments, with dabigatran having the additional option of removal from the blood system via haemodialysis.<sup>18,19</sup> To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® as a specific reversal agent to dabigatran.<sup>20,21</sup> Results from clinical trials to date show Praxbind® to be a highly specific reversal agent with a favourable safety profile.<sup>22–25</sup>

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