HAUTE AUTORITÉ DE SANTÉ

CARDIOLOGY
Update
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TRANSPARENCY COMMITTEE OPINION SUMMARY

# **PRAXBIND** (idarucizumab), dabigatran neutralising agent

**High clinical benefit for emergency neutralisation of the anticoagulant effect of dabigatran and minor clinical improvement, only in cases where no therapeutic alternative is available**

## Main points

- PRAXBIND is a specific neutralising agent of the anticoagulant effect of dabigatran (PRADAXA), a direct thrombin inhibitor. PRAXBIND binds with dabigatran with a very strong affinity, approximately 300 times stronger than that of dabigatran for thrombin. It specifically neutralises the anticoagulant effect of dabigatran without interfering with other oral anticoagulants.
- It has MA for adults treated with dabigatran when rapid neutralisation of its anticoagulant effects is required for a surgical emergency or urgent procedures or in case of uncontrolled or life-threatening bleeding.
- The data available do not allow an estimation of the direct impact of PRAXBIND in terms of morbidity and mortality compared to the conventional treatment.

## Therapeutic strategy

- There are no formalised and validated guidelines available to date on the management of severe bleeding or urgent procedures for patients treated with direct oral anticoagulants (DOACs). In these two scenarios, management is guided by specific plasma DOAC assay results or, in downgraded mode, with routine haemostasis tests.
- According to the clinical status, the management of bleeding in patients treated with dabigatran is based on symptomatic treatments (haemostatic procedures, vascular filling, haemodynamic correction, blood transfusion, etc.), haemostatic medicinal products, prothrombin complexes and idarucizumab.
  In the event of a surgical procedure or need for an urgent invasive procedure on a patient treated with dabigatran, the choice between idarucizumab and other measures is particularly dependent on the bleeding risk associated with the procedure and the time since the last dose was administered.
- Dialysis is among the forms of treatment proposed in some cases.

### Role of the medicinal product in the therapeutic strategy

PRAXBIND is a first-line medicinal product, only when rapid neutralisation of the anticoagulant effects of dabigatran is needed:

- in the event of uncontrolled or life-threatening bleeding,
- for a surgical emergency or urgent procedures (time to procedure < 8 hours).

The decision to administer PRAXBIND should account for various parameters such as the location and seriousness of the bleeding, plasma concentration of dabigatran, time since the last dose, kidney function, etc.: therefore, it should not be used systematically to treat any type of bleeding.

The same applies for urgent surgical procedures, which do not require systematic PRAXBIND administration, particularly in case of procedures with a low bleeding risk or if dabigatran plasma concentration is known and very low.

If PRAXBIND is not available, prothrombin complexes, activated or not, may be proposed, off-label, as alternatives except in the case of some invasive procedures with a very high bleeding risk (depending on the case: perimedullary anaesthesia or deep nerve block, lumbar puncture, intravenous thrombolysis).

Non-specific supportive treatments (depending on the case, mechanical compression, haemostatic procedure, transfusion, vascular filling, other haemostatic agents, etc.) have an important role in overall management and may be sufficient to prevent bleeding. PRAXBIND is combined with these non-specific measures.

## Clinical data

- New data are based on the final findings of a non-controlled, non-randomised, prospective case study including 503 patients: 301 with bleeding requiring neutralisation (group A) and 202 patients requiring surgery within an 8-hour interval (group B). The profile of the patients included as well as the findings of the final analyses were similar to those described for the intermediate analysis (123 patients included).
- Intracranial and gastrointestinal bleeding represented most of the grounds for inclusion in the bleeding group (45.5% and 32.6% respectively). Complete neutralisation was observed within 4 hours following the infusion of idarucizumab for 98.5% of patients assessable using the dilute thrombin time and 94.8% of patients assessable using the ecarin clotting time (primary analyses). Neutralisation of the anticoagulant effect of dabigatran was observed within minutes following administration. Eight patients received an additional dose and one received two additional doses of idarucizumab. Over 50% of the patients received a haemostatic treatment in parallel, essentially packed red blood cells. Clotting factors, CCP or FVIIa, were administered to 5.8% of patients (7% in group A) and tranexamic acid to 8.5% of patients (11.6% in group A). Dialysis was set up for 7.4% of patients.
- In the surgery group, the patient's haemostasis was considered by the surgeon to be "normal" with the use of idarucizumab for 93.4% of the assessable procedures (n=197),
- Approximately 20% of the patients included died before the end of the 90-day follow-up period, with a similar incidence in both groups and in particular a death rate of 24.5% (n=24/98) among those treated for intracranial bleeding and 16% among those with gastrointestinal bleeding. Almost half of the deaths occurred in the first 5 days.
- The latest data and the pharmacovigilance did not allow the identification of any new safety signals.

## Special prescription requirements

- Medicinal product for hospital use only
- Reserved for emergency use

## Benefit of the medicinal product

- The actual clinical benefit* of PRAXBIND is high
- In the therapeutic strategy in respect of the management of patients requiring rapid reversal of the anticoagulant effects of dabigatran, PRAXBIND:
  - provides an improvement in actual clinical benefit** (IACB IV, minor) only in cases where no therapeutic alternative is available (certain urgent invasive procedures: perimedullary anaesthesia or deep nerve block, lumbar puncture, intravenous thrombolysis),
  - does not provide an improvement in actual clinical benefit** (IABC V) in other cases (other urgent invasive procedures and uncontrolled or life-threatening bleeding).
- Approved for retention of hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 13 June 2018 (CT-16401) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"