**SCHEDULING STATUS:** S4

## 1. NAME OF THE MEDICINE

**Praxbind®**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 50 mL contains 2,5 g idarucizumab.

Sugar free.

Contains 2 g of sorbitol and 25 mg sodium per vial – see section 4.4.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for infusion

Clear to slightly opalescent, colourless to slightly yellow solution, essentially free from foreign particles, but may contain a few translucent, white to whitish product typical particles.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PRAXBIND is a specific reversal agent for dabigatran and is indicated in patients treated with PRADAXA (dabigatran etexilate) when rapid reversal of the anticoagulant effects of dabigatran is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

### 4.2 Posology and method of administration

**Posology**

The recommended dose of PRAXBIND is 5 g (2 vials of 2,5 g/50 mL).

In a limited number of patients, recurrence of plasma concentrations of unbound dabigatran and concomitant prolongation of clotting tests have occurred up to 24 hours after administration of PRAXBIND (see section 5.1).

Administration of a second 5 g dose of PRAXBIND may be considered in the following situations:

- recurrence of clinically relevant bleeding together with prolonged clotting times, or

- patients require a second emergency surgery/urgent procedure and have prolonged clotting times.

Relevant coagulation parameters are activated Partial Thromboplastin Time (aPTT), diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT) (see section 5.1).

***Restarting antithrombotic therapy***

PRADAXA (dabigatran etexilate) treatment can be re-initiated 24 hours after administration of PRAXBIND, if the patient is clinically stable and adequate haemostasis has been achieved.

After administration of PRAXBIND, other antithrombotic therapy (e.g. low-molecular weight heparin) can be started at any time, if the patient is clinically stable and adequate haemostasis has been achieved.

Absence of antithrombotic therapy exposes patients to the thrombotic risk of their underlying disease or condition.

***Renal impairment***

No dose adjustment is required in renally impaired patients. Renal

impairment did not impact the reversal effect of idarucizumab (as in PRAXBIND) (see section 5.2).

***Hepatic impairment***

An impact of hepatic impairment, assessed by hepatic injury as determined by elevated liver function tests, on the pharmacokinetics of idarucizumab has not been observed. No dose adjustment is required in patients with hepatic injury.

***Geriatric patients/Sex/Race***

Based on population pharmacokinetic analyses, sex, age and race do not have a clinically meaningful effect on the pharmacokinetics of idarucizumab (as in PRAXBIND).

***Paediatric patients***

The safety and efficacy of PRAXBIND in the paediatric population has not been established.

**Method of administration**

PRAXBIND (2 vials of 2,5 g/50 mL) is administered intravenously, as two

consecutive infusions over 5 to 10 minutes each or as a bolus injection.

For additional instructions for use and handling see section 6.6.

## 4.3 Contraindications

None.

## 4.4 Special warnings and precautions for use

Idarucizumab (as in PRAXBIND) binds specifically to dabigatran and reverses its anticoagulant effect. It will not reverse the effects of other anticoagulants (see section 5.1).

PRAXBIND treatment can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

### *Traceability*

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient file.

### *Hypersensitivity*

The risk of using PRAXBIND in patients with known hypersensitivity (e.g.

anaphylactoid reaction) to idarucizumab or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment. If an anaphylactic reaction or other serious allergic reaction occurs, administration of PRAXBIND should be discontinued immediately and appropriate therapy initiated.

***Hereditary fructose intolerance***

The recommended dose of PRAXBIND contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance, parenteral administration of sorbitol has been associated with reports of hypoglycaemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function and death. Therefore, in patients with hereditary fructose intolerance the risk of treatment with PRAXBIND must be weighed against the potential benefit of such an emergency treatment.

***Sodium content***

This medicinal product contains 2,2 mmol (or 50 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

***Thromboembolic Events***

Patients being treated with dabigatran have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate (see section 4.2).

**Urinary protein testing**

Praxbind causes transient proteinuria as a physiologic reaction to renal protein overflow after bolus/short term application of 5 g idarucizumab intravenously. The transient proteinuria is not indicative of renal damage, which should be taken into account for urine testing.

## 4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies with PRAXBIND and other medicinal products have been performed. Based on the pharmacokinetic properties and the high specificity in binding to dabigatran, clinically relevant interactions with other medicinal products are considered unlikely.

Preclinical investigations have shown no interactions with volume expanders, coagulation factor concentrates and anticoagulants other than dabigatran (see section 5.1).

## 4.6 Fertility, pregnancy and lactation

The safety of PRAXBIND in pregnancy and lactation has not been established.

## 4.7 Effects on ability to drive and use machines

Not relevant.

## 4.8 Undesirable effects

In a phase III trial the safety of PRAXBIND has been evaluated in 503 patients, who had uncontrolled bleeding or required emergency surgery or procedures and were under treatment with PRADAXA, as well as in 224 volunteers in phase I trials.

No adverse reactions have been identified.

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X

SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

## 4.9 Overdose

***Symptoms***

There is no clinical experience with overdoses of PRAXBIND.

The highest dose of PRAXBIND studied in healthy subjects was 8 g. No safety signals have been identified in this group.

***Treatment***

If symptoms of overdosage should occur, treatment is symptomatic and supportive.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

CATEGORY AND CLASS: A 30.1 Antibodies

***Mode of action***

Idarucizumab is a specific reversal agent for dabigatran. It is a humanised monoclonal antibody fragment (Fab) that binds to dabigatran with very high affinity, approximately 300-fold more potent than the binding affinity of dabigatran for thrombin. The idarucizumab-dabigatran complex is characterised by a rapid on-rate and extremely slow off-rate resulting in a very stable complex. Idarucizumab potently and specifically binds to dabigatran and its metabolites and neutralises their anticoagulant effect.

***Clinical Trials***

Three randomised, double-blind, placebo-controlled Phase I studies in 283 subjects (224 treated with idarucizumab) were conducted to assess the safety, efficacy, tolerability, pharmacokinetics and pharmacodynamics of idarucizumab, given alone or after administration of dabigatran etexilate. The investigated population consisted of healthy subjects and subjects exhibiting specific population characteristics covering age, body weight, race, sex and renal impairment. In these studies the doses of idarucizumab ranged from 20 mg to 8 g and the infusion times ranged from 5 minutes to 1 hour.

Representative values for pharmacokinetic and pharmacodynamic parameters were established on the basis of healthy subjects aged 45-64 years receiving 5 g idarucizumab.

One prospective, open-label, non-randomized, uncontrolled study (RE-VERSE AD) was conducted to investigate the treatment of adult patients who presented with dabigatran-related life-threatening or uncontrolled bleeding (Group A) or who required emergency surgery or urgent procedures (Group B). The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, based on central laboratory determination of dilute Thrombin Time (dTT) or Ecarin Clotting Time (ECT). A key secondary endpoint was the restoration of haemostasis.

RE-VERSE AD included data for 503 patients: 301 patients with serious bleeding (Group A) and 202 patients requiring an urgent procedure/surgery (Group B). Approximately half of the patients in each group were male. The median age was 78 years and the median creatinine clearance was 52,6 mL/min. 61,5 % of patients in Group A and 62,4 % of patients in Group B had been treated with dabigatran 110 mg twice daily.

Reversal was only evaluable for those patients showing prolonged coagulation times prior to idarucizumab treatment. Most patients, in both Groups A and B, achieved complete reversal of the anticoagulant effect of dabigatran (dTT: 98,7 %; ECT: 82,2 %; aPTT: 92,5 % of evaluable patients, respectively) in the first 4 hours after administration of 5 g idarucizumab. Reversal effects were evident immediately after administration.

Figure 1 – Reversal of dabigatran-induced clotting time prolongation determined by dTT in patients from the RE-VERSE AD study (N = 487)

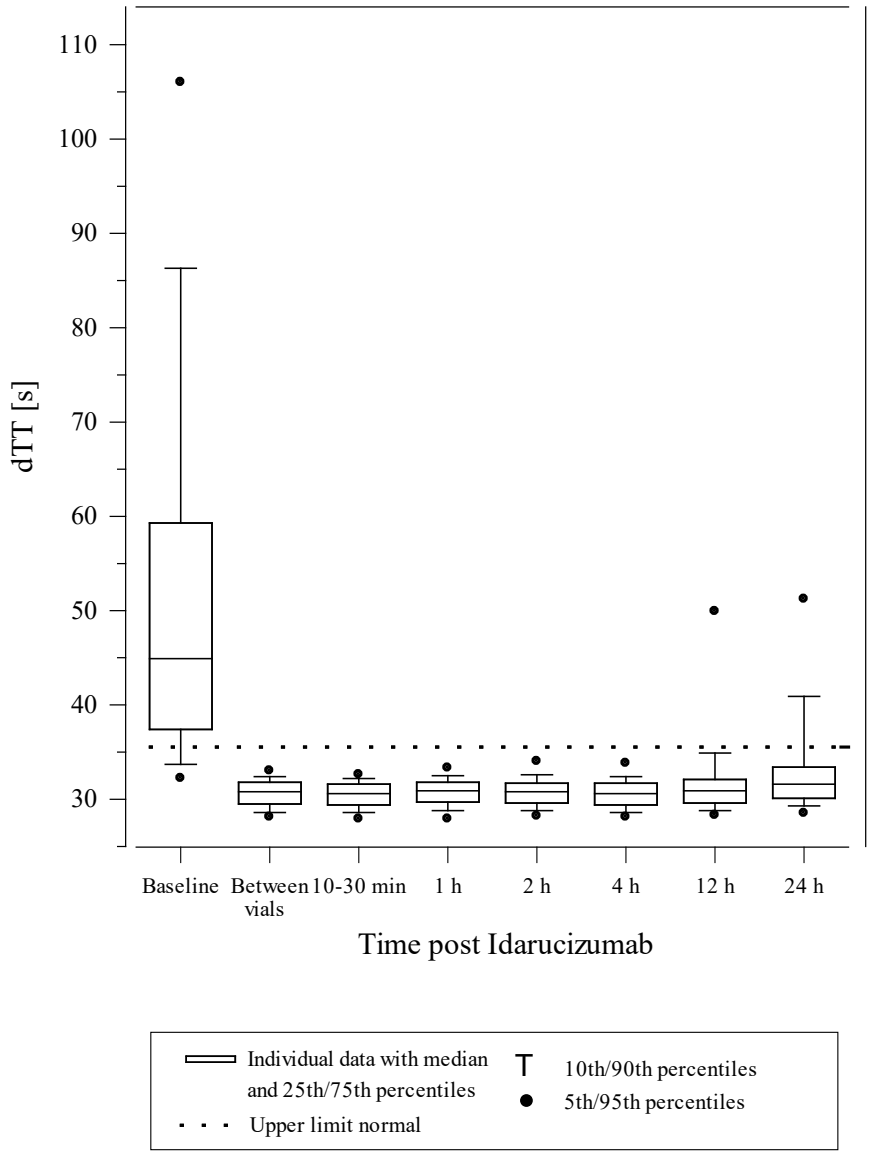



Figure 2 – Reversal of dabigatran-induced clotting time prolongation determined by ECT in patients from the RE-VERSE AD study (N = 487)

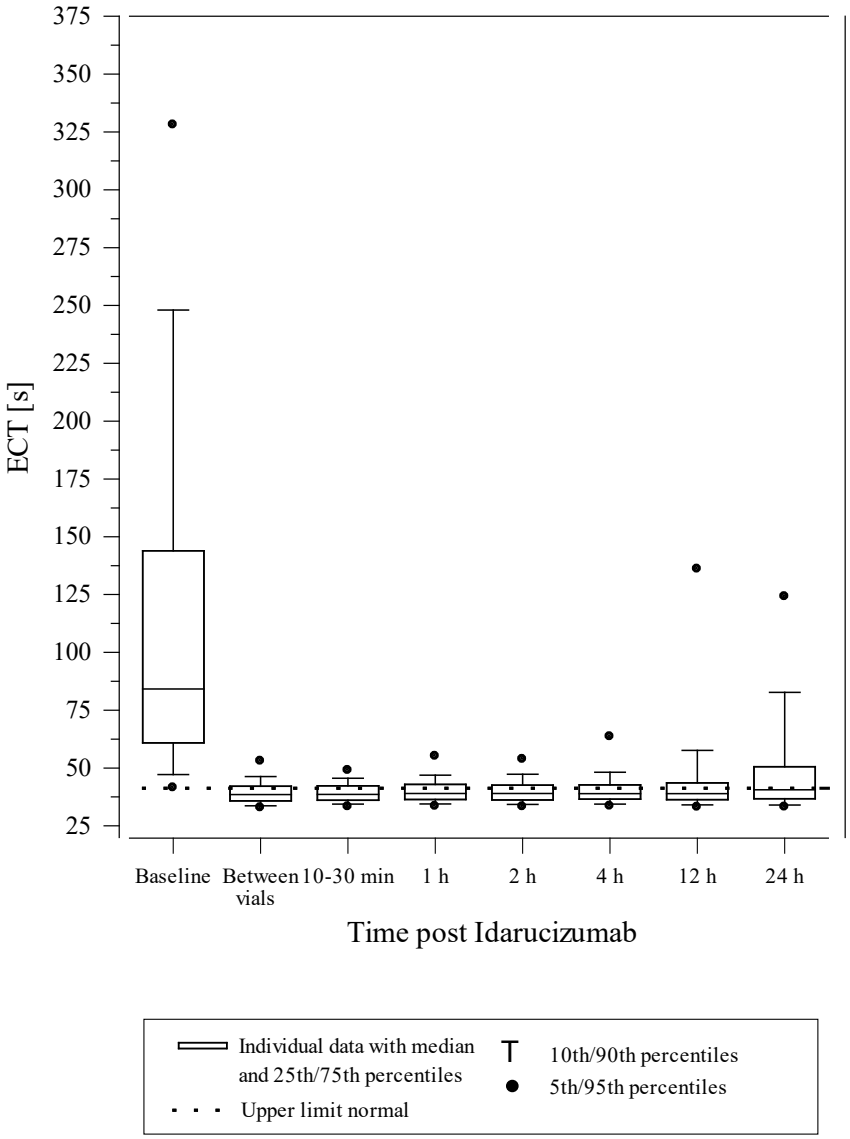
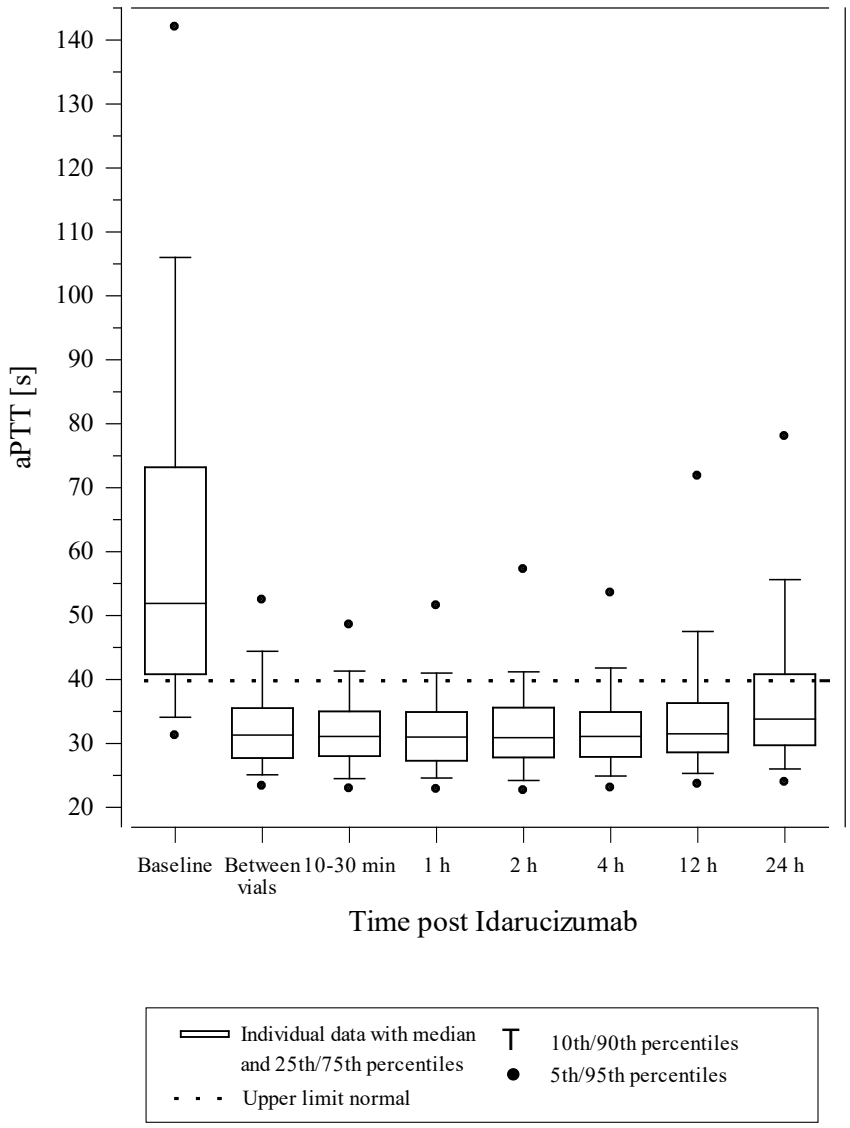



Figure 3 – Reversal of dabigatran-induced clotting time prolongation determined by aPTT in patients from the RE-VERSE AD study (N = 486)




Restoration of haemostasis was achieved in 80,3 % of evaluable patients who had serious bleeding and normal haemostasis was observed in 93,4 % of patients who required an urgent procedure.

Of the total 503 patients, 101 patients died; each of these deaths could be

attributed either as a complication of the index event or associated with co-morbidities. Thrombotic events were reported in 34 patients (23 out of the 34 patients were not on antithrombotic therapy at the time of the event) and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient. Mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported. A causal relationship to idarucizumab could not be established.

***Pharmacodynamic effects***

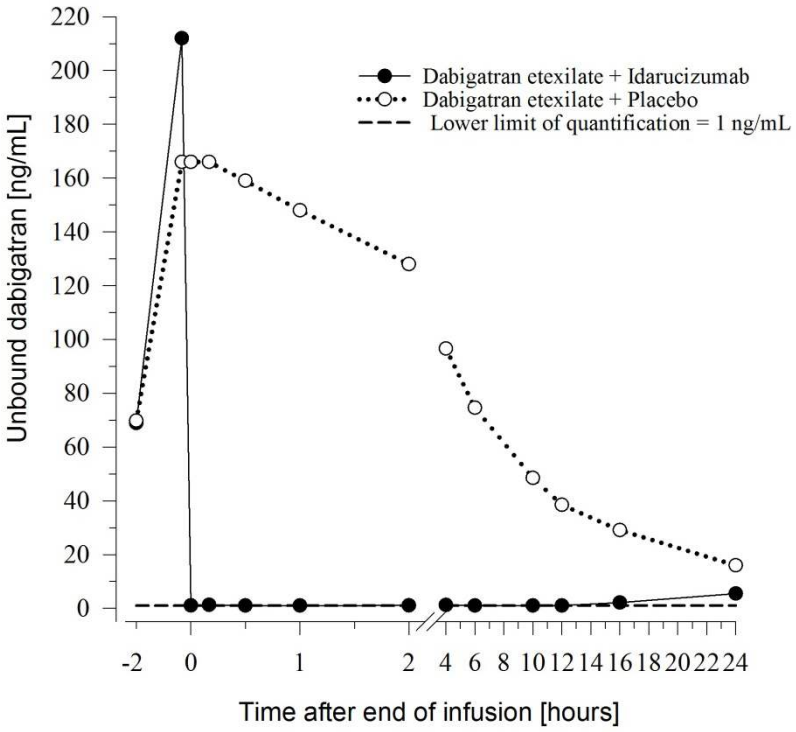
The pharmacodynamics of idarucizumab after administration of dabigatran etexilate were investigated in healthy subjects aged 45 to 64 years receiving a dose of 5 g as intravenous infusion. The median peak dabigatran exposure in the investigated healthy subjects was in the range of a twice daily administration of 150 mg dabigatran etexilate in patients.

***Effect of idarucizumab on the exposure and anticoagulant activity of dabigatran***

Immediately after the administration of idarucizumab, the plasma concentrations of unbound dabigatran were reduced by more than 99 %, resulting in levels with no anticoagulant activity.

The majority of the patients showed sustained reversal of dabigatran plasma concentrations up to 12 hours (≥ 90 %). In a subset of patients, recurrence of plasma levels of unbound dabigatran and concomitant elevation of clotting tests was observed, possibly due to re-distribution of dabigatran from the periphery. This occurred 1 - 24 hours after administration of idarucizumab, mainly at timepoints ≥ 12 hours.

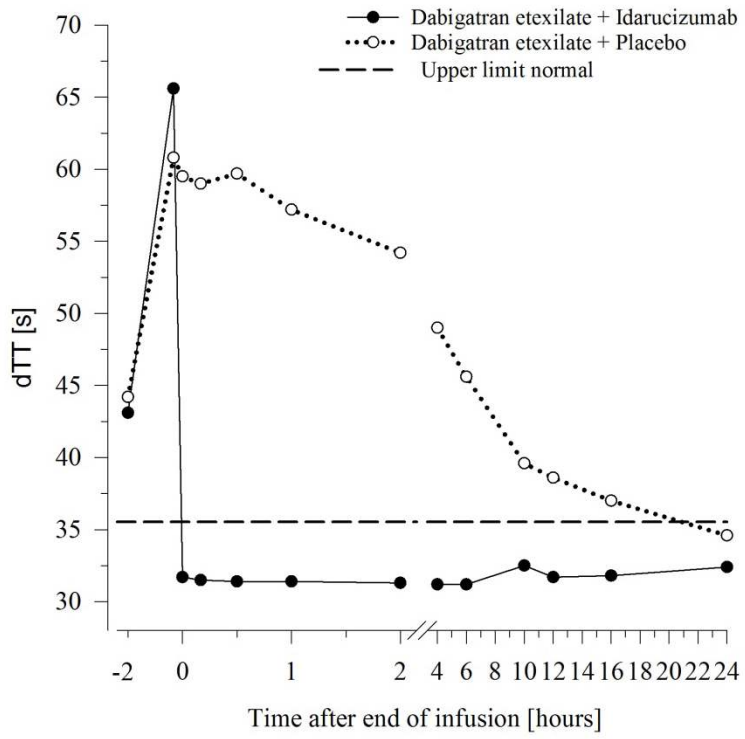
Figure 4 – Plasma-levels of unbound dabigatran in the representative group of healthy subjects (administration of idarucizumab or placebo at 0 h)




Dabigatran prolongs the clotting time of coagulation markers such as diluted Thrombin Time (dTT), Thrombin Time (TT), activated Partial Thromboplastin Time (aPTT) and Ecarin Clotting Time (ECT), which provide an approximate indication of the anticoagulation intensity. A value in the normal range after administration of idarucizumab indicates that a patient is no longer anticoagulated. A value above the normal range may reflect residual active dabigatran or other clinical conditions, e.g. presence of other medicines or transfusion coagulopathy. These tests were used to assess the anticoagulant effect of dabigatran. A complete and sustained reversal of dabigatran-induced clotting time prolongation was observed immediately after the idarucizumab infusion, lasting over the entire

observation period of at least 24 h.

Figure 5 – Reversal of dabigatran-induced clotting time prolongation determined by dTT in the representative group of healthy subjects (administration of idarucizumab or placebo at 0 h)




***Thrombin generation parameters***

Dabigatran exerts pronounced effects on parameters of the Endogenous Thrombin Potential (ETP). Idarucizumab treatment normalised both thrombin lag time ratio and time to peak ratio to baseline levels as determined 0,5 to 12 hours after the end of the idarucizumab infusion.

Idarucizumab alone has shown no procoagulant effect measured as ETP. This suggests that idarucizumab has no prothrombotic effect.

***Re-administration of dabigatran etexilate***

24 hours after the idarucizumab infusion, re-administration of dabigatran etexilate resulted in expected anticoagulant activity.

***Immunogenicity***

Serum samples from 283 subjects in phase I trials (224 volunteers treated with idarucizumab) and 501 patients were tested for antibodies to idarucizumab before and after treatment. Pre-existing antibodies with cross-reactivity to idarucizumab were detected in approximately 12 % (33/283) of the phase I subjects and 3,8 % (19/501) of the patients. No impact on the pharmacokinetics or the reversal effect of idarucizumab or hypersensitivity reactions were observed.

Treatment-emergent possibly persistent anti-idarucizumab antibodies with low titres were observed in 4 % (10/224) of the phase I subjects and 1,6 % (8/501) of the patients suggesting a low immunogenic potential of idarucizumab. In a subgroup of 6 phase I subjects, idarucizumab was administered a second time, two months after the first administration. No anti-idarucizumab antibodies were detected in these subjects prior to the second administration. In one subject, treatment-emergent anti-idarucizumab antibodies were detected after the second administration. Nine patients were re-dosed with idarucizumab. All nine patients were re-dosed within 6 days after the first idarucizumab dose. None of the patients re-dosed with idarucizumab tested positive for anti-idarucizumab antibodies.

***Preclinical pharmacodynamic properties***

A trauma model in pigs was performed using a blunt liver injury after dosing with dabigatran to achieve supratherapeutic concentrations of about 10 fold of human plasma levels. Idarucizumab effectively and rapidly reversed the life-threatening bleeding within 15 min after the injection. All pigs survived at idarucizumab doses of approximately 2,5 and 5 g. Without idarucizumab, the mortality in the anticoagulated group was 100 %.

Preclinical investigations with idarucizumab have shown no interactions with

- volume expanders
- coagulation factor concentrates, such as prothrombin complex concentrates (PCCs, e.g. 3 factor and 4 factor), activated PCCs (aPCCs) and recombinant factor VIIa
- other anticoagulants (e.g. thrombin inhibitors other than dabigatran, Factor Xa inhibitors including low-molecular weight heparin, vitamin K-antagonists, heparin). Thus idarucizumab will not reverse the effects of other anticoagulants.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of idarucizumab were investigated in healthy subjects aged 45 to 64 years receiving a dose of 5 g, as intravenous infusion.

### *Distribution*

Idarucizumab exhibited multiphasic disposition kinetics and limited extravascular distribution. Following the intravenous infusion of a 5 g dose, the geometric mean volume of distribution at steady state ($V_{ss}$) was 8,9 L (geometric coefficient of variation (gCV) 24,8 %). In the terminal phase, the

volume of distribution ($V_z$) was 41,8 L (gCV 22,3 %).

***Biotransformation***

Several pathways have been described that may contribute to the metabolism of antibodies. All of these pathways involve biodegradation of the antibody to smaller molecules, i.e. small peptides or amino acids which are then reabsorbed and incorporated in the general protein synthesis.

***Elimination***

Idarucizumab was rapidly eliminated with a total clearance of 47,0 mL/min (gCV 18,4 %), an initial half-life of 47 minutes (gCV 11,4 %) and a terminal half-life of 10,3 h (gCV 18,9 %). After intravenous administration of 5 g idarucizumab, 32,1 % (gCV 60,0 %) of the dose was recovered in urine within a collection period of 6 hours and less than 1 % in the following 18 hours.

The remaining part of the dose is assumed to be eliminated via protein catabolism, mainly in the kidney.

After treatment with idarucizumab proteinuria has been observed. The transient proteinuria is a physiologic reaction to renal protein overflow after bolus/short term application of 5 g idarucizumab intravenously. The transient proteinuria usually peaked about 4 hours after idarucizumab administration and normalised within 12 - 24 hours. In single cases the transient proteinuria persisted for more than 24 hours.

***Renal impairment***

In Phase I studies PRAXBIND has been investigated in subjects with a creatinine clearance ranging from 44 to 213 mL/min. Subjects with a creatinine clearance below 44 mL/min have not been studied in Phase I. Depending on the degree of renal impairment the total clearance was reduced compared to healthy subjects, leading to an increased exposure of idarucizumab (as in PRAXBIND).

Based on pharmacokinetic data from 347 patients with different degrees of renal function (median creatinine clearance 21 – 99 mL/min) it is estimated that mean idarucizumab exposure ($AUC_{0-24h}$) increases by 38 % in patients with mild (CrCl 50 - <80 mL/min), by 90 % in moderate (30 - <50 mL/min) and by 146 % in severe (0 - <30 mL/min) renal impairment. Since dabigatran is also excreted primarily via the kidneys, increases in the exposure to dabigatran are also seen with worsening renal function.

Based on these data and the extent of reversal of the anticoagulant effect of dabigatran in patients, renal impairment does not impact the reversal effect of idarucizumab.

***Hepatic impairment***

Idarucizumab has been studied in 58 patients with varying degrees of hepatic impairment. Compared to 272 patients without hepatic impairment, the median AUC of idarucizumab was changed by -6 %, 37 % and 10 % in patients with AST/ALT elevations of 1 to <2 x ULN (N=34), 2 to <3 x ULN (N=3) and >3 x ULN (N=21), respectively. Based on pharmacokinetic data from 12 patients with liver disease, the AUC of idarucizumab was increased by 10 % as compared to patients without liver disease.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Polysorbate 20, sodium acetate trihydrate, sorbitol and water for injection.

### 6.2 Incompatibilities

PRAXBIND must not be mixed with other medicinal products.

### 6.3 Shelf life

4 years.

Once solution has been removed from the vial, chemical and physical in-use stability of idarucizumab has been demonstrated for 6 hours at room temperature. The solution should not be exposed to light for more than 6 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at or below 30 °C, unless the method of opening precludes the risk of microbial contamination.

## 6.4 Special precautions for storage

Store in a refrigerator (2 – 8 ˚C). Do not freeze. Keep the containers in the outer carton in order to protect from light.

Prior to use, the unopened vial may be kept at room temperature (at or below 30 °C) for up to 48 hours, if stored in the original package in order to protect from light.

PRAXBIND may be exposed to conditions at or below 25 ˚C for a maximum period of 3 months during transportation and handling.

Keep out of reach of children.

For storage conditions after opening of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Two clear, colourless 50 mL glass vials with grey rubber stoppers and secured with blue aluminium flip-off caps, each bearing a label with

integrated hanger, packed in a printed cardboard carton with the professional information and patient information leaflet.

## 6.6 Special precautions for disposal and other handling

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

PRAXBIND must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of PRAXBIND. The line must be flushed with sterile sodium chloride 9 mg/mL (0,9 %) solution prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

PRAXBIND is for single-use only and does not contain preservatives.

No incompatibilities between PRAXBIND and polyvinyl chloride, polyethylene or polyurethane infusion sets or polypropylene syringes have been observed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Ingelheim Pharmaceuticals (Pty) Ltd

Suite 1, Building 4, 2nd Floor

Waterfall Corporate Campus

74 Waterfall Drive

Midrand

South Africa

## 8. REGISTRATION NUMBER

50/30.1/0315

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 09 December 2019

Date of revision of the text: 19 April 2024

## 10. DATE OF REVISION OF THE TEXT

23 May 2025

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| BOTSWANA Reg. No. | S2 |

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| PRAXBIND | BOT1803382 | |
| NAMIBIA Reg. No. | | NS2 |
| PRAXBIND | 19/30.1/0053 | |

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