ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Praxbind 2.5 g/50 mL solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection/infusion contains 50 mg idarucizumab.

Each vial contains 2.5 g idarucizumab in 50 mL.

Idarucizumab is produced by recombinant DNA technology in Chinese hamster ovary cells.

Excipients with known effect

Each vial contains 2 g sorbitol and 25 mg sodium in 50 mL (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion

Clear to slightly opalescent, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required:

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

4.2 Posology and method of administration

Restricted to hospital use only.

Posology

The recommended dose is 5 g idarucizumab (2 vials of 2.5 g/50 mL).

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

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

- recurrence of clinically relevant bleeding together with prolonged clotting times, or
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed, 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).

A maximum daily dose has not been investigated.

Restarting antithrombotic therapy

Dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

After administration of idarucizumab, 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.

Special populations

Elderly

No dose adjustment is required in elderly patients aged 65 years and above (see section 5.2).

Patients with renal impairment

No dose adjustment is required in renally impaired patients. Renal impairment did not impact the reversal effect of idarucizumab (see section 5.2).

Patients with hepatic impairment

No dose adjustment is required in patients with hepatic injury (see section 5.2).

Paediatric population

The safety and efficacy of Praxbind in children below the age of 18 years have not been established. Currently available data are described in section 5.1.

Method of administration

Intravenous use.

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 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 the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 hypoglycemia, 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. If Praxbind is administered in these patients, intensified medical care during Praxbind exposure and within 24 hours of exposure is required.

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 (see section 5.2). The transient proteinuria is not indicative of renal damage, which should be taken into account for urine testing.

Sodium content

This medicinal product contains 50 mg sodium per dose, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products 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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data for the use of idarucizumab in pregnant women. Reproductive and developmental toxicity studies have not been performed, given the nature and the intended clinical use of the medicinal product. Praxbind may be used during pregnancy, if the expected clinical benefit outweighs the potential risks.

Breast-feeding

It is unknown whether idarucizumab/metabolites are excreted in human milk.

Fertility

There are no data on the effect of idarucizumab on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

In a phase III study 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 (dabigatran etexilate), as well as in 224 volunteers in phase I studies. Furthermore, 359 patients were enrolled in a global idarucizumab administration surveillance program to collect data on usage patterns in a real-world-setting. One paediatric patient was treated in the context of a paediatric safety trial.

No adverse reactions have been identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no clinical experience with overdoses of idarucizumab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: all other therapeutic products, antidotes, ATC code: V03AB37

Mechanism 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.

Pharmacodynamic effects

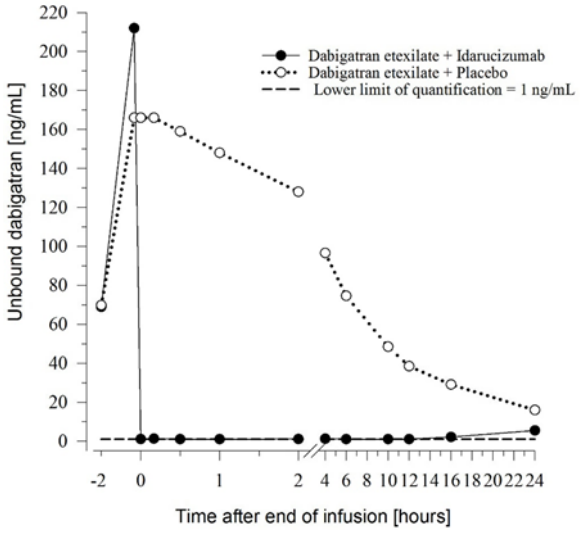
The pharmacodynamics of idarucizumab after administration of dabigatran etexilate were investigated in 141 subjects in phase I studies, of which data for a representative subgroup of 6 healthy subjects aged 45 to 64 years receiving a dose of 5 g as intravenous infusion are presented. The median peak 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 times 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 1. 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 dTT, TT, aPTT and 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 active substances 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 2. 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)

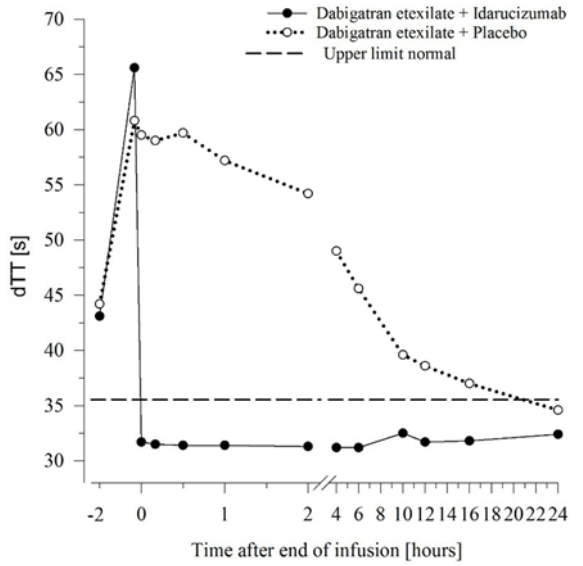
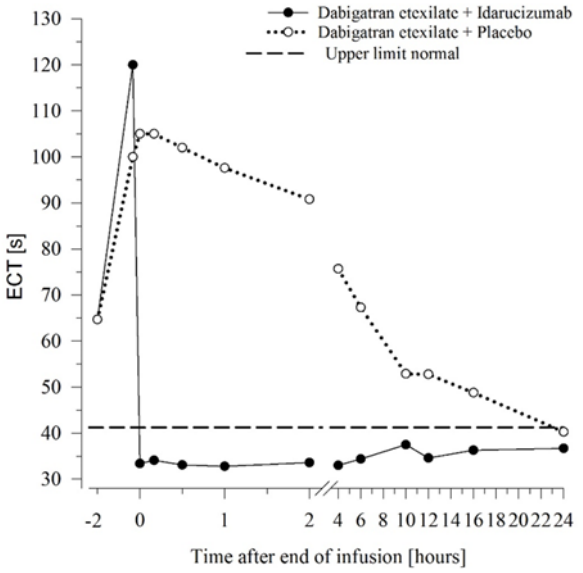


Figure 3. Reversal of dabigatran-induced clotting time prolongation determined by ECT in the representative group of healthy subjects (administration of idarucizumab or placebo at 0 h)



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.

Preclinical pharmacodynamics

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%.

Clinical efficacy and safety

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 (see sections 5.1 and 5.2).

One prospective, open-label, non-randomised, 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 dTT or 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 (CrCl) 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 4. Reversal of dabigatran-induced clotting time prolongation determined by dTT in patients from the RE-VERSE AD study (N = 487)

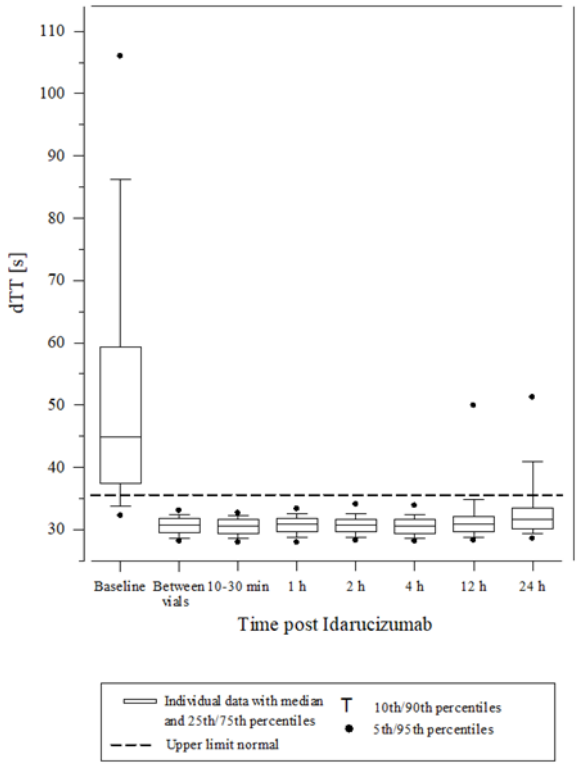


Figure 5. Reversal of dabigatran-induced clotting time prolongation determined by ECT in patients from the RE-VERSE AD study (N = 487)

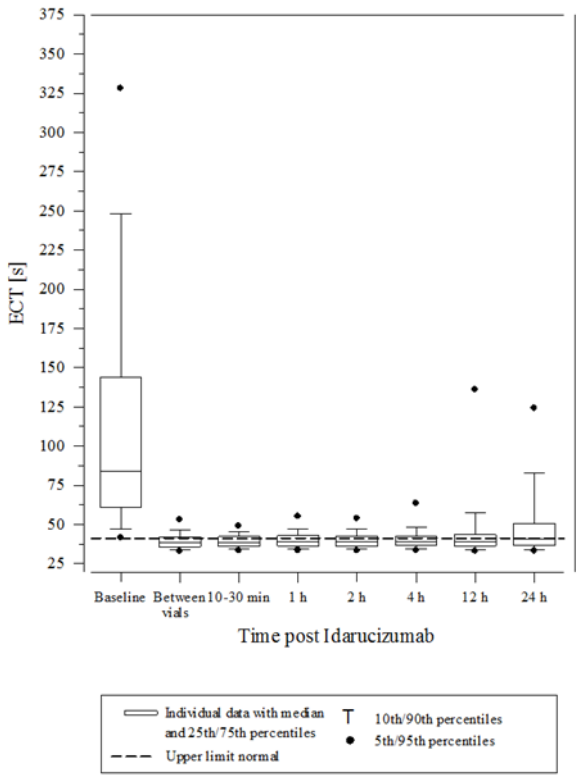
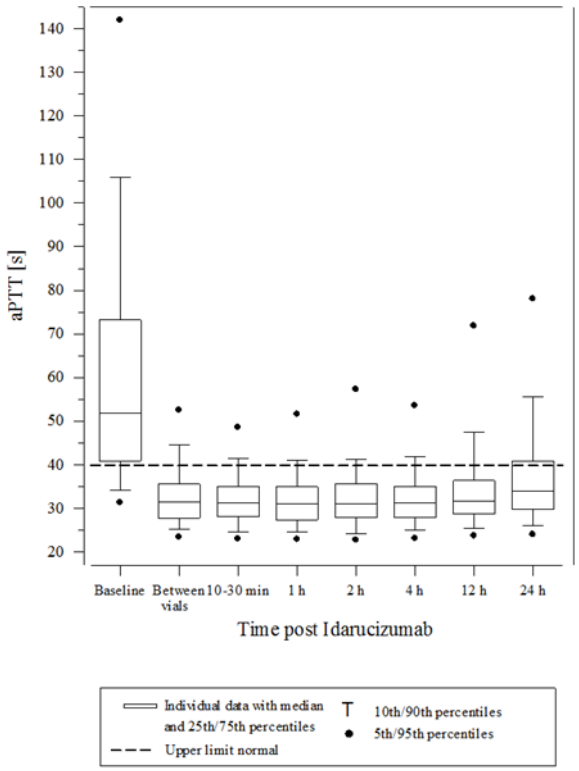


Figure 6. Reversal of dabigatran-induced clotting time prolongation determined by aPTT in patients from the RE-VERSE AD study (N = 486)



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.

Paediatric population

One paediatric patient was included in a single dose, open label, safety trial of intravenous administration of idarucizumab. The trial enrolled paediatric patients from clinical trials with dabigatran etexilate for the treatment and secondary prevention of venous thromboembolism (VTE). For inclusion, patients required rapid reversal of the anticoagulant effect of dabigatran. The patient (between 16-< 18 years old) was treated with dabigatran etexilate for secondary prevention of VTE due to the presence of a clinical risk factor. A bleeding event required a surgical intervention and adequate haemostasis. Treatment with 5 g idarucizumab resulted in a rapid and complete reversal of the anticoagulant effect of dabigatran. The pharmacokinetics of idarucizumab and its effects on pharmacodynamics were consistent with data obtained in adults.

Immunogenicity

Serum samples from 283 subjects in phase I studies (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 titers 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 9 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of idarucizumab were investigated in 224 subjects in phase I studies, of which data for a representative subgroup of 6 healthy subjects aged 45 to 64 years receiving a dose of 5 g as intravenous infusion are presented.

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 (Vd_{ss}) was 8.9 L (geometric coefficient of variation (gCV) 24.8%).

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 ($t_{1/2}$) of 47 minutes (gCV 11.4%) and a terminal $t_{1/2}$ 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 h after idarucizumab administration and normalised within 12-24 hours. In single cases the transient proteinuria persisted for more than 24 hours.

Patients with 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.

Based on pharmacokinetic data from 347 patients with different degrees of renal function (median CrCl 21-99 mL/min) it is estimated that mean idarucizumab exposure (area under the concentration-time curve (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.

Patients with 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.

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 times the upper limit of normal (ULN) (N = 34), 2 to < 3 times the ULN (N = 3) and > 3 times the 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.

Elderly / Gender / Race

Based on population pharmacokinetic analyses, age, gender and race do not have a clinically meaningful effect on the pharmacokinetics of idarucizumab.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity studies of up to 4 weeks in rats and 2 weeks in monkeys. Safety pharmacology studies have demonstrated no effects on the respiratory, central nervous or cardiovascular system.

Studies to evaluate the mutagenic and carcinogenic potential of idarucizumab have not been performed. Based on its mechanism of action and the characteristics of proteins no carcinogenic or genotoxic effects are anticipated.

Studies to assess the potential reproductive effects of idarucizumab have not been performed. No treatment-related effects have been identified in reproductive tissues of either sex during repeat dose intravenous toxicity studies of up to 4 weeks in the rat and 2 weeks in monkeys. Additionally, no idarucizumab binding to human reproductive tissues was observed in a tissue cross-reactivity study. Therefore, preclinical results do not suggest a risk to fertility or embryo-fetal development.

No local irritation of the blood vessel was observed after i.v. or paravenous administration of idarucizumab. The idarucizumab formulation did not produce haemolysis of human whole blood *in vitro*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium acetate trihydrate (E262)
acetic acid (E260, for pH adjustment)
sorbitol (E420)
polysorbate 20 (E432)
water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

After opening the vial, chemical and physical in-use stability of idarucizumab has been demonstrated for 6 hours at room temperature (up to 30 °C).

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the medicinal product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

Store in the original package in order to protect from light.

Prior to use, the unopened vial may be kept at room temperature (up to 30 °C) for up to 48 hours, if stored in the original package in order to protect from light. The solution should not be exposed to light for more than 6 hours (in unopened vial and/or in-use).

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

6.5 Nature and contents of container

50 mL solution in a glass vial (type I glass), with a butyl rubber stopper, an aluminium cap and a label with integrated hanger.

Pack size of 2 vials.

6.6 Special precautions for disposal and other handling

Parenteral medicinal products such as Praxbind 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 sodium chloride 9 mg/ml (0.9%) solution for injection 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 (see section 6.3).

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. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1056/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2015
Date of latest renewal: 27 July 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
GERMANY

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
GERMANY

Boehringer Ingelheim France
100-104 Avenue de France
75013 Paris
FRANCE

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Praxbind 2.5 g/50 mL solution for injection/infusion
idarucizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 50 mL contains 2.5 g idarucizumab.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate (E262), acetic acid (E260), sorbitol (E420), polysorbate 20 (E432), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection/infusion
2 vials of 50 mL each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1056/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

19. OTHER – Printing on inside of lid

- The enclosed package leaflet contains additional information for healthcare professionals.
- The recommended dose of Praxbind is 5 g (2 × 2.5 g/50 mL).

- Intravenous administration as two consecutive infusions over 5 to 10 min each or as bolus injections.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial label

1. NAME OF THE MEDICINAL PRODUCT

Praxbind 2.5 g/50 mL solution for injection/infusion
idarucizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 50 mL contains 2.5 g idarucizumab.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate (E262), acetic acid (E260), sorbitol (E420), polysorbate 20 (E432), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection/infusion
1 vial of 50 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1056/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient and user

Praxbind 2.5 g/50 mL solution for injection/infusion
idarucizumab

Read all of this leaflet carefully, because it contains important information for you. Please note this medicine is mainly used in emergency situations and the doctor will have decided that you needed it.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Praxbind is and what it is used for
2. What you need to know when you receive Praxbind
3. How to use Praxbind
4. Possible side effects
5. How to store Praxbind
6. Contents of the pack and other information

1. What Praxbind is and what it is used for

What Praxbind is

Praxbind contains the active substance idarucizumab. Idarucizumab is a reversal agent specific for dabigatran, a blood thinner medicine that blocks a substance in the body, which is involved in blood clot formation.

Praxbind is used to rapidly trap dabigatran in order to inactivate its effect.

What Praxbind is used for

Praxbind is used in adults in emergency situations where your doctor decides that rapid inactivation of the effect of dabigatran is required:
- For emergency surgery/urgent procedures;
- In life-threatening or uncontrolled bleeding.

2. What you need to know when you receive Praxbind

Warnings and precautions

Talk to your doctor or nurse before receiving Praxbind:
- if you are allergic to idarucizumab or to any other of the substances listed in section 6.
- if you have a genetic disease called hereditary fructose intolerance. In this case, the substance sorbitol contained in this medicine may cause serious adverse reactions.

They will take this into account before treating you with Praxbind.

This medicine will only remove dabigatran from your body. It will not remove other medicines used to prevent the formation of blood clots.

After dabigatran has been removed from your body, you are not protected from the formation of blood clots. Your doctor will continue treating you with medicines used to prevent the formation of blood clots as soon as your medical condition allows.

Children and adolescents

There is no information on the use of Praxbind in children.

Other medicines and Praxbind

Tell your doctor if you are taking, have recently taken or might take any other medicines.

This medicine has been designed to only bind to dabigatran. It is unlikely that Praxbind will influence the effect of other medicines or that other medicines will influence Praxbind.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine.

There is no information on the effects of this medicine in pregnant or breast-feeding women. Praxbind does not affect any functions in the body as such, so your doctor may decide to give you this medicine, if the expected benefits outweigh any potential risks.

Praxbind contains sodium

This medicine contains 50 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 2.5% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Praxbind

This medicine is for hospital use only.

The recommended dose is 5 g (2 vials of 2.5 g/50 mL).

In rare cases you may still have too much dabigatran in your blood after a first dose of this medicine and your doctor may decide to give you a second 5 g dose in specific situations.

Your doctor or nurse will give you this medicine by injection or infusion into a vein.

After you have received this medicine, your doctor will decide on the continuation of your treatment to prevent blood clot formation. Dabigatran can be given again 24 hours after administration of this medicine.

Detailed instructions for your doctor or nurse on how to administer this medicine can be found at the end of this package leaflet (see ‘Handling instructions’).

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine may cause side effects, although not everybody gets them.

Until now, no side effects have been identified.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in

Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Praxbind

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

Store in the original package in order to protect from light.

Once opened, this medicine is intended for immediate use.

6. Contents of the pack and other information

What Praxbind contains

- The active substance is idarucizumab.
- The other ingredients are: sodium acetate trihydrate (E262), acetic acid (E260, for pH adjustment), sorbitol (E420), polysorbate 20 (E432) and water for injections.

What Praxbind looks like and contents of the pack

Praxbind is a clear to slightly opalescent, colourless to slightly yellow solution supplied in a glass vial closed with a butyl rubber stopper and an aluminium cap.

Each pack contains two vials.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Praxbind binds specifically to dabigatran and reverses its anticoagulant effect. It will not reverse the effects of other anticoagulants.

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

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

The recommended dose of Praxbind contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance there is a risk for serious adverse reactions, which must be weighed against the benefit of an emergency treatment with Praxbind. If Praxbind is administered in these patients, intensified medical care during Praxbind exposure and within 24 hours of exposure is required.

Dosage and administration:

The recommended dose is 5 g idarucizumab (2 vials of 2.5 g/50 mL).

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

- recurrence of clinically relevant bleeding together with prolonged clotting times, or
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed, 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).

A maximum daily dose has not been investigated.

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.

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.

Dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

After administration of idarucizumab, 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.

Handling instructions:

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 sodium chloride 9 mg/mL (0.9%) solution for injection 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.

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

physical in-use stability of idarucizumab has been demonstrated for 6 hours at room temperature (up to 30 °C). The solution should not be exposed to light for more than 6 hours (in unopened vial and/or inuse).

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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