Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for idarucizumab

Proprietary Product Name: Praxbind

Sponsor: Boehringer Ingelheim Pty Ltd

October 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADA	anti-drug antibody/ies
AE	adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AUC	area under the plasma drug concentration-time curve
AUC_{t1-t2}	area under the plasma drug concentration-time curve from t1 to t2
bid	bis in die (twice daily)
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum serum concentration of drug
CMI	Consumer Medicine Information
DE	dabigatran etexilate
EMA	European Medicines Agency
Fab	fragment antigen binding
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HC	heavy chain
IC50	half maximal inhibitory concentration
IV	intravenous(ly)
LC	light chain
OD	once daily
PD	pharmacodynamic(s)
PI	Product Information

Abbreviation	Meaning
PK	pharmacokinetic(s)
RMP	Risk Management Plan
SAE	serious adverse event
t½	elimination half life
Tmax	Time taken to reach the maximum concentration (Cmax)
Vd	volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	New biological medicine
Decision:	Approved
Date of decision:	10 May 2016
Date of entry onto ARTG	11 May 2016
Active ingredient:	Idarucizumab
Product name:	Praxbind
Sponsor's name and address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Road North Ryde NSW 2113
Strength:	2.5 g
Container:	Type 1 glass vial
Pack size:	50 mL
Approved therapeutic use:	Praxbind is a specific reversal agent for dabigatran and is indicated in patients treated with dabigatran etexilate (Pradaxa) when rapid reversal of the anticoagulant effects of dabigatran is required: • for emergency surgery/urgent procedures; • in life-threatening or uncontrolled bleeding
Route of administration:	Intravenous
Dosage:	5 g (two 50 mL vials = 2 x 2.5 g)
ARTG number:	237761

Product background

This AusPAR describes the application by Boehringer Ingelheim Pty Ltd to register a new biological entity idarucizumab (trade name, Praxbind[1]) as a specific reversal agent for dabigatran. Idarucizumab is a humanised fragment antigen binding (Fab) molecule derived from an IgG1 isotype molecule, directed against dabigatran. The proposed indication is:

> *Praxbind/Pradturn 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*

[1] Also called "Pradturn" in this AusPAR.

- *in life-threatening or uncontrolled bleeding.*

Each 50 mL vial of solution for injection/infusion contains 2.5 g of idarucizumab (50 mg/mL). The recommended dose is 5 g. Two 50 mL vials (2 x 2.5 g) constitute one complete dose. The complete dose of 5 g is administered intravenously (IV), as two consecutive infusions over 5 to 10 minutes each or as a bolus injection. Pradaxa can be re-initiated 24 h after administration of Praxbind, if the patient is clinically stable and adequate haemostasis has been achieved. After administration of Praxbind, other antithrombotic therapy (for example, 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.

The Advisory Committee on Prescription Medicines (ACPM) has not considered idarucizumab previously but has considered dabigatran on several occasions. The Advisory Committee on the Safety of Medicines (ACSOM) considered the safety aspects of idarucizumab and the Risk Management Plan (RMP) at meeting 30 in November 2015.

Regulatory status

The international regulatory status at the time of submission is listed in Table 1.

Table 1. International regulatory status at time of submission.

Country	Submission date	Status
United States	19 February 2015	Approved, 16 October 2015
Europe (Centralised procedure)	2 March 2015	Approved, 20 November 2015
New Zealand	13 March 2015	Approved, 10 December 2015
Canada	26 February 2015	Under review
Switzerland	15 April 2015	Under review
Singapore	30 October 2015	Under review

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

The active substance of Praxbind/Pradturn, idarucizumab, is a humanised murine Fab fragment whose target is the direct thrombin inhibitor dabigatran. The Fab molecule binds to dabigatran with a higher affinity than dabigatran binds to thrombin.

Idarucizumab solution for injection/infusion (50 mg/mL) is a clear to slightly opalescent, colourless to slightly yellow solution presented as a nominal 50.0 mL fill volume in a 50 mL Type 1 glass vial in buffered, isotonic, preservative free solution.

Idarucizumab is a humanised murine Fab fragment directed against the thrombin inhibitor, dabigatran.

The idarucizumab molecule is composed of the light chain (LC, amino acids 1-219) and heavy chain (HC, amino acids 1-225) fragment, covalently linked together by one disulphide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain. Additional intramolecular disulfide bonds are formed between cysteine 23 and cysteine 93 of the light chain (variable region), cysteine 139 and cysteine 199 of the light chain (constant region), and between cysteine 22 and cysteine 95 of the heavy chain (variable region) and cysteine 149 and cysteine 205 of the heavy chain (constant region).

Molecular formula

Based on the predicted amino acid sequence, the molecular formula of the disulfide bonded idarucizumab Fab molecule is $C_{213}1H_{3299}N_{555}O_{671}S_{11}$.

Molecular weight/molecular mass

The predicted molecular mass of idarucizumab corresponding to the formula above is 47,766 Da. It consists of one LC polypeptide of theoretical average molecular weight of 24,043 Da (reduced) and one HC fragment polypeptide of theoretical average molecular weight of 23,733 Da (reduced).

Drug substance (active ingredient)

Idarucizumab drug substance is a colourless to slightly yellow, clear to slightly opalescent solution.

The physicochemical characteristics are as follows:

- pH: 5.5 (formulated drug substance)
- Melting point: 84.4°C
- Isoelectric point: 9.4 or 9.5 (experimentally)
- Extinction coefficient: 1.54 cm^2 * at 280 nm
- Other characteristics: humanised Fab derived from murine IgG1 isotype one κ LC and one γ HC fragment one inter chain disulfide bond at Cys225 of HC and Cys219 of LC four Cys residues on each HC and LC forming intra disulfide bridges HC N-terminal glutamine is nearly completely cyclised to pyroglutamate.

Biological properties

Idarucizumab is directed against the direct thrombin inhibitor dabigatran. Idarucizumab binds to dabigatran with a higher affinity than that of thrombin. The biological activity of idarucizumab is determined by a thrombin clotting assay. The reversal of the anti coagulatory effect of dabigatran can be monitored by measuring the clotting after adding idarucizumab to a mixture of synthetic thrombin and fibrinogen.

Immunological properties

Idarucizumab binds dabigatran in a concave region at the interface of the variable domains. All CDR loops except L2 are involved in dabigatran binding.

Drug substance manufacture

Idarucizumab is expressed in Chinese hamster ovary (CHO) cells. It is manufactured using standard mammalian cell culture techniques, followed by a series of protein purification steps including several chromatography steps, as well as steps for removal and inactivation of potential viruses.

The cell culture process begins with thawing a vial of the working cell bank (WCB). During multiple inoculum cultivation steps in shaker and rocking bag bioreactors in selective medium, the cells are repeatedly sub-cultivated (passaged) to provide sufficient cells to seed a production bioreactor which is operated in a fed batch mode to generate sufficient cell mass and product concentration.

Purification and formulation of idarucizumab consists of a series of chromatographic steps (affinity, anion and cation exchange chromatography), virus inactivation, virus filtration, concentration and buffer exchange by tangential flow filtration and final filtration through a filter.

The sponsor proposed a shelf life of 30 months at -20°C. Stability data have been generated under real time and stressed conditions to characterise the stability profile of the substance and to establish a shelf life. Due to insufficient stability data, the recommended shelf life for the drug substance is 18 months when stored at -20°C, with a three months mid-term storage conditions at 2-8°C.

Drug product

Idarucizumab drug product manufacturing includes thawing of formulated drug substance, sterile filtration and filling, capping, visual inspection, labelling, and secondary packaging. All formulation is completed as part of drug substance manufacture.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

The product is not photostable. The proposed shelf life is 30 months when stored at 2-8°C. In-use stability data have also been submitted. Due to insufficient stability data, the recommended shelf life for the drug product is 24 months when stored at 2-8°C with 3 months for processing and handling of drug product at 25°C.

Biopharmaceutics

Biopharmaceutics data are not required as the product is administered by intravenous injection or infusion.

Quality summary and conclusions

Good Manufacturing Practice (GMP) clearance was initially outstanding for one manufacturing site.

On 5 April 2016, GMP clearance was updated. There are no outstanding GMP issues, hence, no objection to registration on quality grounds.

III. Nonclinical findings

Introduction

The scope of the nonclinical strategy was consistent with published guidelines.[2] Although the complete battery system of Good Laboratory Practice (GLP) safety pharmacology studies was not provided, many of the relevant organ systems were examined in the general repeat dose toxicity studies. Overall, the quality of studies included in the nonclinical dossier was high and the nonclinical testing strategy appropriate for the proposed conditions of clinical use.

Pharmacology

Primary pharmacology

Idarucizumab is a humanised Fab fragment antibody that binds to the direct thrombin inhibitor, dabigatran, to neutralise its anticoagulant activity. Efficacy was assessed in a number of investigations that examined affinity and selectivity of idarucizumab, while in vitro and in vivo studies demonstrated neutralisation of the anticoagulant effects of dabigatran.

The in vitro (and ex vivo) studies reported the following findings:

- Idarucizumab has high affinity for dabigatran (Kd ≤ 62 pM, pH ≥ 6) and does not bind with Factors V, VIII & XIII, fibrinogen, von Willebrand Factor, PAR-1 peptide or protein C; idarucizumab (± dabigatran) did not exhibit binding with human plasma or serum albumin
- Idarucizumab reversed anticoagulant activity of dabigatran (and its acyl glucuronidated metabolite) in human whole blood (IC50 11.3 nM) or plasma (IC50 3.1-11 nM); idarucizumab itself did not exhibit any independent prothrombotic activity; Effects were specific for dabigatran with no neutralising effect observed against rivaroxaban, apixaban, hirudin, argatroban, heparin or enoxaparin induced anticoagulation

In vivo studies utilised mouse, rat and pig models of haemostasis with animals pre-dosed with dabigatran to evoke anticoagulation with altered coagulation parameters serving as indices of haemostatic changes. Salient findings of these studies were as follows:

- Idarucizumab alone had no effect on coagulation parameters (for example, Thrombin Time [TT] and activated Partial Thromboplastin Time [aPTT]) in animal models

[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals", July 1997.

- Idarucizumab rapidly reversed dabigatran mediated anticoagulation in animals pretreated with dabigatran (mouse and rat tail bleed models, in mouse model of intracerebral haemorrhage and in pig blunt liver trauma model)
- Onset of reversal was apparent within minutes of idarucizumab dosing; neutralisation persisted for up to 30 mins in rats concomitantly infused with dabigatran
- Idarucizumab increased plasma levels of total dabigatran (inclusive of antibody-bound dabigatran and its metabolites) in all animal models; attributed to dabigatran redistributing from the extravascular space into blood vessels to bind with free idarucizumab
- Extent of neutralisation depends on stoichiometric considerations: if idarucizumab levels are less than equimolar to dabigatran, anticoagulant activity gradually re-emerges because extravascular dabigatran redistributes into circulation and is not affected by already bound idarucizumab
- In rats, the prolonged bleeding time elicited by dabigatran was slightly augmented by antiplatelet agents ticagrelor and clopidogrel; idarucizumab prevented the prolonged bleeding attributed to dabigatran but did not affect the antiplatelet agent effects or anticoagulant activity of warfarin and enoxaparin
- Idarucizumab given to dabigatran treated animals within 15 minutes of acute injury improved survival rates and prevented extensive blood loss, as well as normalised coagulation parameters, MAP, platelet counts, haemoglobin and fibrinogen levels
- Haemodilution and substances used as volume expanders to treat hypovolaemia (for example, 6% HES, 4% gelatin) did not interfere with the interaction between dabigatran and idarucizumab

Overall, pharmacodynamic studies demonstrated selective binding of idarucizumab to dabigatran (as well as its active glucuronidated metabolites) which reverses the anticoagulant actions of dabigatran.

One potential concern is the very high affinity of idarucizumab for dabigatran (Kd 2.1 pM, compared to affinity of dabigatran for thrombin 0.7 nM) and whether this might present a prothrombotic risk. However, idarucizumab alone has no pharmacological activity under either in vitro or in vivo conditions. Moreover, some of the repeat dose toxicity studies monitored prothrombotic marker levels before and after idarucizumab administration and found no difference from levels in vehicle treated animals. Animal studies also indicated that stoichiometric considerations are important to the interaction between dabigatran and idarucizumab, such that plasma levels of antibody should be equimolar or in excess of dabigatran to sustain neutralisation of dabigatran, since in some studies a gradual return of anticoagulant activity was apparent.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacology studies were submitted. A number of the primary pharmacology studies reported no activity of idarucizumab against well-known anticoagulant and anti-platelet agents. Furthermore, a tissue cross reactivity study against a panel of human and animal tissue found no evidence of reactivity of idarucizumab. As a substance exerting its actions solely within the vascular milieu, there is no evidence suggesting that idarucizumab interacts with anything other than its antigen (dabigatran).

Safety pharmacology assessment consisted of a dedicated GLP study on the respiratory system as well as CNS (Irwin test observations) and cardiovascular system (electrocardiograph waveform analyses) monitoring in some of the GLP repeat dose toxicity studies. No treatment related effects were noted for idarucizumab and overall there were no adverse findings suggestive of adverse effects on organ systems.

Pharmacokinetics

Pharmacokinetic parameters of idarucizumab were investigated in rats and Rhesus monkeys in the presence and absence of dabigatran and were compared to clinical data from healthy volunteers, elderly volunteers and patients with mild and moderate renal impairment. Dabigatran was always administered at least 15 minutes prior to idarucizumab dosing to ensure that anticoagulation was taking place.

Absorption and distribution

As a Fab fragment antibody substance, idarucizumab is intended for intravenous administration only and therefore has 100% bioavailability with peak plasma levels attained almost immediately following dosing. A dose escalating study in monkeys (Study No. DDB0127/11r090) tested three doses of idarucizumab and found plasma levels increased in a dose proportionate manner with no difference in exposure between male and females. Dabigatran dosing did not affect plasma idarucizumab. The plasma concentration time profile of idarucizumab exhibited biphasic kinetics with a rapid initial decline (short initial half-life; 0.2-0.75 h in all species) that paralleled distribution into the circulation, while the second phase showed a slower, more prolonged elimination phase (terminal half-life; 4.3-5.8 h in all species). Clearance of idarucizumab was similar across all species (0.6-2.3 mL/min/kg) and the volume of distribution at steady state was small (approximately equivalent to plasma volume,) confirming that idarucizumab exerts its actions strictly within the vascular milieu. Antibodies against idarucizumab were detected in all animal species that received multiple doses but did not appear to significantly affect exposure and efficacy of idarucizumab.

Plasma levels of (total) dabigatran were however affected by idarucizumab, with levels increasing ~ 2 fold when in the presence of idarucizumab (Study No. DM-13-1030/U13-3577-01). This effect was due to the emergence of dabigatran from the extravascular space in excess of that participating in anticoagulation. Because renal function plays a significant role in idarucizumab excretion (and also dabigatran), studies on rats models of renal impairment (5/6 nephrectomised rats) were also conducted. This animal model showed elevations in plasma exposures for both idarucizumab and dabigatran, relative to sham operated counterpart animals (Ratio of 2.32 and 1.89 folds of sham-operated animals, respectively).

Distribution

No specific studies were conducted to examine tissue distribution of idarucizumab. In view of the low volume of distribution noted across all species, idarucizumab is not likely to distribute in tissue compartments other than within the vasculature. A study on cryosections of tissues from rats, monkeys and humans found no evidence of cross reactivity with idarucizumab and therefore idarucizumab is not expected to form complexes and deposits in tissues, even within the vascular milieu.

Metabolism

No specific studies on metabolism were conducted but it is anticipated that it undergoes protein catabolism similarly to other protein based pharmaceuticals.

Excretion

In rats and monkeys, a small percentage of idarucizumab (~10-20%) was found to be excreted through urine unchanged. The remaining amount was likely also excreted through urine as catabolised protein, as expected for protein based pharmaceuticals. In humans extent of excretion was dependent on dose with ~10% of dose excreted

unchanged at 1 g idarucizumab, while at 4 g the amount was ~40%, an effect attributed to the saturable nature of renal tubule reuptake for catabolism.

Conclusion

Overall, there were sufficient similarities in the pharmacokinetic profiles of idarucizumab in rats, monkeys and humans (especially monkeys and humans) for these species to suitable serve as adequate models for the toxicity tests.

Pharmacokinetic drug interactions

No specific studies on drug interaction potential of idarucizumab were conducted.

Toxicology

Acute toxicity

A single dose toxicity study was conducted in rats that received one of two doses of idarucizumab (50 and 175 mg/kg, IV) or drug diluent (50 mM sodium acetate and 200 mM sorbitol). There were no toxicological findings reported and all animals survived the till the term of observation period (14 days). Thus, overall idarucizumab exhibited a low order of acute toxicity.

Repeat dose toxicity

Repeat dose toxicity studies were conducted in rats and Rhesus monkeys, using the clinical route (IV administration). Studies were up to 4 weeks in rats and 2 weeks in monkeys. As an antidote to a chronically used active pharmaceutical, idarucizumab has single use only application, although the need for a second exposure may potentially arise. For short term use biopharmaceuticals, such as idarucizumab, the published guidelines[3] suggests that studies up to 2 weeks duration are sufficient to support marketing authorisation; thus, the length of the studies in this submission is adequate.

Relative exposure

A comparative assessment of systemic exposure of idarucizumab from clinical studies against the animal values is in Table 2. Human reference values are taken from several studies and included data from different patient groups, including elderly patients and patients with impaired renal function. Relative exposures attained in the animal studies (as AUC) were moderately low.

[3] European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals Step 5 (EMA/CHMP/ICH/731268/1998)", June 2011.

Table 2. Systemic exposure of idarucizumab from clinical studies.

			Clinical exposure multiples			
			Healthy volunteers		Renal impairment	
			45 – 64 yrs[1]	> 64 yrs[2]	Mild [3]	Moderate[4]
Study No. DDB0136 (11R091) Rat (Wistar Han)NOAEL: 500 mg/kg/day, IV	500 mg/kg, IV	C_{max}: 181500 nM	7	6	6	7
		AUC: 107500 nM	3	2	2	2
Study No. U12-3328 Monkey	150 mg/kg, IV	C_{max}: 48750 nM	2	2	2	2
		AUC: 49400 nM	1	1	1	1
	500 mg/kg, IV	C_{max}: 235000 nM	9	8	7	9
		AUC: 223000 nM	6	5	4	3
Study No. U13-3376 Monkey	no dabigatran	C_{max}: 159750 nM	6	6	5	6
		AUC: 173157 nM	5	4	3	3
	dabigatran	C_{max}: 163000 nM	7	6	5	6
		AUC: 171000 nM	5	4	3	3
Study No. n00230533 Monkey	no dabigatran	C_{max}: 174500 nM	7	6	5	7
		AUC: 202000 nM	5	5	4	3
	dabigatran	C_{max}: 172500 nM	7	6	5	7
		AUC: 202000 nM	5	5	4	3

1. Study No. c02742738 (Trial No. 1321.2) – Healthy volunteers 45-64 yrs, 5 g/day IV, C_{max}: 25000 nM, $AUC_{0-\infty}$: 37000 nM.h
2. Study No. c02742738 (Trial No. 1321.2) – Healthy volunteers > 64 yrs, 5 g/day IV, C_{max}: 28300 nM, $AUC_{0-\infty}$: 43900 nM.h

3. Study No. c02742738 (Trial No. 1321.2) – Renal impairment, mild, 5 g/day IV, C_{max}: 32100 nM, $AUC_{0-\infty}$: 53100 nM.h
4. Study No. c02742738 (Trial No. 1321.2) – Renal impairment, moderate, 5 g/day IV, C_{max}: 25600 nM, $AUC_{0-\infty}$: 67900 nM.h

Major toxicities

There were no major toxicity findings in any of the repeat-dose studies.

In the rat study, significant treatment related changes to haematological and serum chemistry parameters were reported. However, these differences were slight and did not result in any adverse outcomes in the test animals nor did they correspond to any notable or related post mortem findings; these are not regarded as toxicologically significant. As expected, immunogenicity occurred in both dose groups (150 and 500 mg/kg/day) at the end of treatment (Days 28 to 30) and at the end of recovery (Day 57); however, there was a slightly higher rate of false positives (average ~13% positive samples in pre-dosed animals).

In the monkey studies, idarucizumab doses of up to 500 mg/kg/day IV (with or without dabigatran treatment) did not cause any treatment related effects. Increased thymus weights relative to control groups were noted in all groups that received idarucizumab in a 2 day study that was followed by a 2 week recovery period (Study No. DDB0230). Treated animals in the recovery group did not show any difference to control animals, indicating that the change in thymus weight was reversible. However, there were no corresponding gross or histopathological changes in the thymus of affected animals and there were no similar observations made in other monkey studies that used a similar or longer dosing regimen. Therefore, this is unlikely to be toxicologically significant. One male treated with idarucizumab (500 mg/kg/day, IV) and dabigatran in a 2 day dosing study (Study No. U12-3328-01) exhibited renal function changes with elevations in plasma urea, creatinine and phosphorus, decreased plasma sodium, potassium and chloride and dilated cortical tubules. This finding prompted further examination of kidney tissue and function (Study No. DDB0230 and DDB0331) since idarucizumab is excreted via urinary excretion directly or as catabolised protein. However, neither of these studies found any treatment related findings of note; the latter study conducted additional immunohistochemical assessments of kidney sections and found no evidence of immune complex formation by idarucizumab within the proximal tubule epithelium.

Immunogenicity was also noted in all of the monkey studies. None of the animals from the main repeat dose toxicity studies showed any hypersensitivity reactions. However, one monkey from a PD/PK study (Study No. DM-12-1103/DDB0210/U13-3539-01) displayed clinical signs indicative of a hypersensitivity reaction (increased respiratory rate, heart rate and pale mucous membranes) upon receiving a third dose of idarucizumab (30 and 60 mg/kg, IV) and was subsequently euthanised. The animal developed antibodies against idarucizumab after intermittent dosing over a one month period. In contrast, although animals that received daily dosing of idarucizumab also developed anti idarucizumab antibodies, none exhibited signs of an adverse immunogenic reaction under the conditions of study. It is therefore unclear whether the intermittent pattern of exposure precipitated hypersensitivity in this animal. The clinical use of idarucizumab is not normally expected to occur more than once, although its use during surgical procedures could conceivably necessitate repeat use. However, the immunogenic reactivity to humanised protein in animal species is not predictive of a corresponding response in humans, and given the isolated incidence of hypersensitivity reaction in an animal species, the immunogenic potential of idarucizumab in humans is likely to be low.

Overall, the observations in both test species were generally benign with findings being mainly associated with the method of administration (injection site reaction) in all groups.

Genotoxicity and carcinogenicity

The genotoxic potential of idarucizumab was not examined in dedicated nonclinical studies, which is acceptable according to ICH guidelines.[4]

The absence of carcinogenicity studies is also acceptable since idarucizumab is not intended for chronic use and standard lifetime rodent studies would not provide useful information or be feasible because of the likely antibody development following repeat administration.

Reproductive toxicity

The sponsor did not conduct any reproductive toxicity studies on idarucizumab on the basis that it is indicated as an antidote under emergency medical conditions and therefore considerations about foetal exposure are likely to be secondary to treating a life-threatening condition. Although not explicitly contraindicated in use during pregnancy, the PI for dabigatran etexilate (Pradaxa) advises against use during pregnancy. Thus the sponsor's justification for not conducting reproductive toxicity studies based on the unlikelihood of pregnant women taking dabigatran etexilate and the single-use, emergency indication of idarucizumab, is acceptable.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2.[5] In the absence of animal reproductive toxicity data, the low likelihood of use during pregnancy and the fact that Fab fragment antibody is unlikely to interact with the FcRn receptor to enable placental transfer to the developing foetus, the proposed category is considered appropriate.

Local tolerance

A dedicated investigation on local tolerance was conducted in rabbits where idarucizumab was injected into the peri venous milieu and monitored for reactivity. No dermal reactions were noted or treatment related macro or histological observations reported. Similarly, none of the general toxicity studies found evidence of local tolerance reactions, as injection site reactions (haemorrhage and/or inflammation at the site of administration) were common to all groups including vehicle treated animals. Overall, idarucizumab is not anticipated to evoke tolerance reactions within the peri venous milieu.

Paediatric use

No specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The quality of studies was high and the nonclinical testing strategy was appropriate for the proposed product and its prescribed conditions of use (that is, single dose use).
- Idarucizumab affinity for dabigatran (Kd ≤ 62 pM at pH ≥ 6) was higher than the affinity of dabigatran for thrombin (Kd 0.7 nM). Anticoagulant activity of dabigatran and its acyl glucuronidated active metabolites was reversed by idarucizumab in whole blood and plasma. Idarucizumab did not reverse rivaroxaban, apixaban, hirudin,

[4] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)", 16 July 1997.

[5] Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

argatroban, heparin or enoxaparin induced anticoagulation and did not exhibit pharmacological/prothrombotic activity on its own.

- Idarucizumab rapidly reversed dabigatran mediated anticoagulation in animal bleed models. It did not affect the activity of antiplatelet agents (ticagrelor, clopidogrel) or anticoagulants (warfarin, enoxaparin). Haemodilution and volume expanders (for example, 4% hydroxyethyl starch) did not affect dabigatran binding with idarucizumab.
- Total plasma dabigatran increased following idarucizumab dosing due to redistribution of extravascular dabigatran back into the circulation, where it is available to interact with idarucizumab. For this reason stoichiometric considerations are important to the interaction between dabigatran and idarucizumab, such that plasma levels of antibody should be equimolar or in excess of dabigatran to sustain neutralisation of dabigatran, since in some animal model studies a gradual return of anticoagulant activity was noted.
- No adverse findings were reported with idarucizumab in GLP studies on respiratory, cardiovascular and CNS systems, therefore clinically relevant effects on these organ systems are not anticipated.
- Intravenously administered idarucizumab exhibited similar pharmacokinetic parameters in the presence and absence of dabigatran in all species, while total dabigatran plasma levels (including bound and unbound) were increased by idarucizumab. Idarucizumab distribution was confined to the vascular milieu. Excretion of idarucizumab was through the urinary route with a small fraction excreted unchanged, while the remainder was through excretion of catabolised protein. Renal impairment increased plasma exposure to both idarucizumab and dabigatran.
- Repeat dose IV toxicity studies of up to 4 weeks in rats and 2 weeks in monkeys found no evidence of systemic toxicity. In the rat, altered haematological and serum chemistry parameters did not correspond to notable post mortem findings. In the monkey, the only adverse findings were from a male from a 2 day dosing study with renal function changes, which did not correspond to treatment related findings of note. Relative exposures attained in the animal studies were low (≥ 6 times the clinical AUC).
- Development of antibodies against idarucizumab was seen in both species. There were no adverse findings in animals from the main repeat dose toxicity studies associated with immunogenic reactions aside from an isolated hypersensitivity reaction in a monkey intermittently dosed with idarucizumab.
- The potential genotoxicity and carcinogenicity of idarucizumab was not examined, which is acceptable according to guidelines on biotechnology-derived products. The absence of reproductive toxicity studies is also acceptable based on the infrequent pattern of use and its proposed use as an antidote under emergency medical conditions.
- Overall there are no nonclinical objections to the registration of idarucizumab (Praxbind/Pradturn). The draft PI should be amended as directed.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Dabigatran etexilate (Pradaxa) is an oral pro drug of dabigatran, a direct-acting thrombin inhibitor that has been shown to be effective in the prevention or reduction of thrombotic events in: patients with non-valvular atrial fibrillation; patients with deep vein thrombosis or pulmonary embolism who have been treated with a parenteral anticoagulant for 5-10 days; patients who have previously received anticoagulant therapy for treatment of venous thromboembolism in orthopaedic surgery patients at risk for post-operative deep vein thrombosis.

Anticoagulation therapy is a mainstay of treatment and prevention of pathologic thrombosis in these different clinical settings. However, as with all anticoagulants, bleeding is a potential side effect especially during emergency surgery or other urgent invasive procedures with dabigatran . In RE-LY, in patients with atrial fibrillation, the annualised rate of emergency surgery was 1.5% and 1.7% for patients treated with dabigatran etexilate 150 mg and dabigatran etexilate 110 mg, respectively. The major bleeding rates in patients treated with dabigatran etexilate 150 mg bid (twice daily) in RE-LY were approximately 3% per year (3 events per 100 patient years), of which half (1.5%) were categorised as life threatening and in rare cases (0.2%), the bleeding was fatal.[6]

To date, acute management of serious bleeding in patients on dabigatran etexilate, including life threatening bleeds, is limited to supportive care, administration of blood or blood products and, in suitable patients, consideration of haemodialysis to remove the drug.[7] Similarly, there are no other alternatives for the management of dabigatran-associated peri-operative bleeds. Until now, there has been no treatment that directly reverses the pharmacological effect of dabigatran. The ability to safely reverse the anticoagulant effect of dabigatran in patients who require rapid reversal could improve the surgical risk of patients requiring emergency surgery, improve the management of serious bleeding events and further increase the overall safety profile of anticoagulation therapy with dabigatran.

Idarucizumab directly, rapidly and specifically neutralises dabigatran's anticoagulant effect due to its very high affinity for dabigatran (Kd = 2.1pM). This affinity is approximately 300 fold higher than the affinity of dabigatran for thrombin (Kd = 0.7 nM). This high affinity for dabigatran means any unbound dabigatran will preferentially bind to idarucizumab. In dynamic equilibrium, any thrombin-bound dabigatran (or other plasma protein-bound dabigatran) will equilibrate with unbound dabigatran and rapidly thereafter be bound by any free idarucizumab. Idarucizumab itself has no known pharmacologic effect and preclinical data have shown that it does not bind to factors in the coagulation cascade or other antithrombotics. The clinical development program consists

[6] Eikelboom JW, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial. *Circulation* 123: 2363-72 (2011).
[7] Weitz JI, et al. Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation 126: 2428-32 (2012). Majeed A, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation* 128: 2325-32 (2013).

of three completed studies in volunteers (Studies 1321.1, 1321.2 and 1321.5) and one ongoing study in patients (1321.3). Each Phase I study in volunteers documented the safety of idarucizumab over a range of doses and also explored the dose response for reversal of dabigatran anticoagulant effect. Clinical studies evaluated pharmacologic reversal of the anticoagulant effect of dabigatran.

Guidance

The strategy of demonstrating reversibility in healthy volunteers, with ratification of a pharmacodynamic endpoint in a small number of patients, in an uncontrolled study in the target indication, was accepted by the European Medicines Agency (EMA) as described in their Scientific Advice letter from November 2013. It was also accepted by Japanese Pharmaceutical and Medical Devices Agency (PMDA) in December 2012 and December 2014, provided that some Japanese patients were included in Study 1321.3. Consultation with US Food and Drug Administration (FDA) in October 2014 indicated that the Agency may consider approval based on a surrogate endpoint in volunteer trials for the assessment of clinical benefit of idarucizumab as a reversal agent for the anticoagulant effect of dabigatran.

> *Comments: In its pre-submission meeting with the TGA dated 25 Nov, 2014, the proposed approach by the sponsors (to demonstrate reversal of dabigatran-induced anticoagulant effect in the 3 Phase 1 studies in healthy volunteers and an ongoing, uncontrolled, open-label, case-series study in patients) was acceptable.*

Contents of the clinical dossier

The submission contained the following clinical information:

- Three clinical pharmacology studies which provided both pharmacokinetic and pharmacodynamic data. Three Phase I studies (1321.1, 1321.2 and 1321.5) in 283 healthy volunteers documented the safety of idarucizumab over a range of doses but also explored the dose-response for reversal of dabigatran anticoagulant effect.
- One population pharmacokinetic analyses (01-02-05).
- One pivotal Phase III efficacy/safety, uncontrolled, open label, case series study (1321.3) which is still ongoing; only interim report (cut off was 2 December 2014) from first 26 patients was provided in this submission. This is the only study in patients evaluating efficacy of idarucizumab in emergency situations, when rapid and safe reversal of the anticoagulant effects of dabigatran is required.
- Pooled analyses of the three Phase I studies in healthy volunteers, integrated summary of efficacy and safety.

  > *Comments: A 4 month safety update summarises safety and efficacy data from this ongoing study and provides data in 123 patients. However, the cover letter, clinical overview and clinical summary of efficacy in the current dossier only summarise data in 26 patients from study 1321.3. The sponsors have been asked to provide clarification on why data from the 123 patients was not included in the summary of efficacy or overview especially considering fact that both FDA and EMA mention data from 123 patients in their approval statements and labelling.*

Paediatric data

The submission did not include paediatric data. As Pradaxa is used in adults only, there is no paediatric data for idarucizumab since the use of idarucizumab in the paediatric population is considered not relevant. A protocol to treat children who may be treated

with dabigatran within a clinical trial is in development, in agreement with the Paediatric Committee (PDCO) in the EU.

Good clinical practice

The trials were carried out in compliance with the clinical trial protocol (CTP), in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH-GCP, and in accordance with applicable regulatory requirements and Boehringer Ingelheim (BI) standard operating procedures (SOPs).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 below shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 3. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	Safety, tolerability, and PKs	1321.1	PKs of IV doses of idarucizumab and to explore the effect of different doses of idarucizumab administered on the steady state PK/PD of dabigatran
		1321.2	PKs and PDs of idarucizumab and to establish the idarucizumab dose(s) effective in reversing dabigatran-induced prolongation of blood coagulation time.
PK in special populations	Healthy Japanese subjects	1321.5	PKs of idarucizumab and to explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran
Population PK analyses	Healthy subjects	01-02-05	Characterise the PopPK of idarucizumab and its binding interaction with dabigatran and to provide PK/PD simulations

* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

- Idarucizumab is a humanised monoclonal antibody fragment, which is administered via IV injection or infusion.

ADME

- Following administration of 5 mg (the proposed dose) of idarucizumab to healthy subjects aged 45 to 64 years the median Tmax (range) of idarucizumab occurred at 0.1 h (0.100-0.250) after dosing.
- Following a 60 min infusion of IV idarucizumab, geometric mean Cmax and AUC0-inf increased proportionally with dose from Cmax values of 79.9 nmol/L (gCV: 15.1%) to 33900 nmol/L (gCV: 13.2%) and from $AUC_{0\text{-}inf}$ values of 146 nmol.h/L (gCV: 19.8%) to 63800 nmol.h/L (gCV: 15.6%) after infusion of 20 mg to 8 g idarucizumab.
- Following administration of a single IV dose of 4 g idarucizumab as a long (60 min, Part 1) or as a short infusion (5 min, Part 2) to healthy males the mean volume of distribution (%gCV) was 6.96 L (17.8) and 8.25 L (26.3), respectively.
- Idarucizumab alone and the idarucizumab-dabigatran complex do not bind to albumin or to other plasma proteins.
- The volume of distribution indicates that idarucizumab is unlikely to be distributed to the tissues.
- The inter subject coefficient of variation values for idarucizumab Cmax and $AUC_{0\text{-}inf}$ following a single 5 g dose in healthy subjects were 16.9% and 18.4%, respectively.
- The estimated inter subject variability on idarucizumab CL, Vc and V2 were 11.9%, 14.8% and 322%, whereas, the estimated proportional and additive residual errors were 0.176 and 0.062, respectively.

Renal impairment

- In subjects with mild renal impairment Cmax and $AUC_{0\text{-}inf}$ were increased approximately 1.28 and 1.44 fold, respectively compared to healthy subjects and for subjects with moderate renal impairment 2.04 and 1.84 fold, respectively compared to healthy subjects.
- Idarucizumab CL was reduced from 47.1 mL/min in healthy subjects to 32.8 mL/min and 25.7 mL/min in subjects with mild and moderate renal impairment, respectively.

Effect of age

- In healthy elderly subjects aged 65 to 80 years, idarucizumab Cmax and $AUC_{0\text{-}inf}$ were increased 1.13 and 1.19 fold, respectively compared to healthy subjects aged 45 to 64 years following a single 5 g dose idarucizumab.
- Idarucizumab CL was reduced from 47.1 mL/min in healthy subjects aged 45 to 64 years to 39.6 mL/min in healthy subjects aged 65 to 80 years.

Japanese subjects

- In Japanese subjects following a 4 g IV infusion, the Cmax and $AUC_{0\text{-}inf}$ of idarucizumab were 28100 nmol/L and 37600 nmol.h/L, respectively. The corresponding values in white males were 15700 nmol/h and 31000 nmol.h/L, respectively indicating that idarucizumab exposure was higher in Japanese subjects than in White subjects.

Effect of dabigatran on idarucizumab PKs

- Overall, the results from the 3 Phase I clinical trials and PopPK study indicate that idarucizumab PKs may be slightly affected by administration with steady state dabigatran (up to 1.20 fold). However, any differences in idarucizumab exposure following administration with or in the absence of dabigatran are unlikely to be clinically significant.

Effect of idarucizumab on dabigatran PKs

- All three Phase I studies indicate that unbound sum dabigatran plasma concentrations decreased to approximately or to below the LLOQ immediately following IV infusion with all 3 doses of idarucizumab (that is, 1 g, 2g and 4 g) and that this decrease was idarucizumab dose dependent.
- The dose dependent decrease in unbound sum dabigatran was accompanied by a idarucizumab dose dependent increase in sum dabigatran.
- Urinary excretion of dabigatran was transiently reduced in the presence of idarucizumab compared to the urinary excretion in absence of idarucizumab.
- Re-exposure to dabigatran 24 h following idarucizumab administration resulted in dabigatran exposure similar to that seen prior to idarucizumab dosing.
- In vitro studies indicate that a range of blood coagulation factors had no effect on the ability of idarucizumab to reverse the effects of dabigatran. Idarucizumab had no effect on the anticoagulant activity of other clinically used agents.
- Results from an in vivo bleeding model indicated that idarucizumab only partially reversed the effects of dabigatran when dabigatran was co-administered with platelet agents.

PopPK analysis

- Idarucizumab disposition after IV administration was best described with a linear, three compartment model and was not influenced by binding to dabigatran.
- PopPK analysis indicated that idarucizumab CL was a function of renal clearance and provided a population median idarucizumab CL of 2.3 L/h. Results indicated that idarucizumab clearance ranged from 1.59 L/h in subjects with renal impairment (CrCL = 40 mL/min) to 2.62 L/h in healthy subjects (CrCL = 120 mL/min).
- In addition, idarucizumab fractional central Vd (3.3 L) was a function of body weight and increased from 0.78 for a 50 kg individual to 1.34 for a 120 kg individual. By contrast, sex, age and body weight were not significantly correlated with idarucizumab clearance after adding CrCL to the model, whereas clearance, was approximately 11% lower in Japanese subjects when compared to non Japanese subjects.

Limitations of PK studies

- Limited PK studies were undertaken in the target population.
- No clinical studies examined the interaction of idarucizumab with drugs other than dabigatran.

Pharmacodynamics

Studies providing pharmacodynamic data

All of the studies that provide PD findings also contain PK data and therefore have been previously summarised in this report.

Evaluator's conclusions on pharmacodynamics

- Idarucizumab acts by selectively and potently binding to dabigatran and thereby reversing dabigatran induced prolongation of blood clotting times.
- In the absence of dabigatran, idarucizumab administration had no effect on coagulation parameters nor did it have a prothrombotic effect.

- Dabigatran consistently prolonged the clotting times of all clotting parameters. In healthy subjects, all doses of idarucizumab tested (1 g to 5 g) resulted in an immediate and complete reversal of dabigatran induced anticoagulant effects. In addition, the duration of the reversal of dabigatran induced elongation of clotting times was dependent on idarucizumab dose with a higher dose of idarucizumab correlating with a longer duration of reversal.
- The duration of the reversal of dabigatran induced dTT elongation was shorter following re-exposure to 2.5 g idarucizumab (2 months following the initial exposure) compared to the initial exposure (up to 4h compared to at least 24 h, respectively), whereas, the duration of reversal of ECT was at least 24 h following both the initial exposure and re-exposure.
- Pre-treatment with dabigatran and restart of dabigatran treatment 24 h after infusion of placebo or idarucizumab to healthy subjects resulted in similar trough and 2 h post dose values of dTT, ECT, aPTT, and TT ratio to baseline.
- Idarucizumab induced reversal of dabigatran anticoagulation was dose dependent in healthy males. For instance, although placebo had no effect on dabigatran induced dTT elongation ($AUEC_{above,2\text{-}12}$ ratio = 1.01), the corresponding ratios following administration of 1 g, 2g or 4 g idarucizumab were 0.26, 0.06 and 0.02, respectively.
- A close linear relationship between unbound sum dabigatran plasma concentration and aPTT, dTT, TT and ECT in healthy Japanese males was identified.
- There appeared to be no influence of sex, age, or renal impairment on the proportion of subjects attaining reversal of dabigatran induced coagulation based on the investigated assays.
- Simulation results, undertaken as part of the PopPK analysis, indicated that CrCL had no effect on the ability of idarucizumab to reverse dabigatran induced elongation of ECT or dTT.

Limitations of PD studies

- No studies examined the secondary PD effects of idarucizumab.
- Repeat dose exposure was only undertaken in 6 healthy subjects and these subjects were only administered half of the dose strength proposed for registration, therefore it is difficult to suggest that these results provide an adequate demonstration of safety and efficacy of idarucizumab with repeat dosing.
- Little to no information is provided regarding idarucizumab antibody formation following re-exposure.
- No studies examined the PD interactions between idarucizumab and drugs other than dabigatran.

Dosage selection for the pivotal studies

Study 1321.1 was a Phase I, randomised, double blind, placebo controlled Phase I study in 157 healthy male volunteers to investigate safety, tolerability and pharmacokinetics of single rising doses (20 mg to 8 g) of idarucizumab (Part 1) and to explore different doses of idarucizumab to reverse dabigatran anticoagulant activity in subjects pre-treated with dabigatran etixilate (Parts 2 and 3). The study design, endpoints, randomisation, blinding and details of the PK and PD results are provided.

In the absence of dabigatran, idarucizumab had no apparent effect on clotting parameters. In Parts 2 and 3, following administration of dabigatran 220 mg BID on Day 1 to Day 3 and 220mg OD on Day 4, median 2 h post dose sum dabigatran concentrations were

comparable with the median exposure previously observed in patients with atrial fibrillation after 150 mg dabigatran etexilate (DE) twice daily dosing. Idarucizumab infusion resulted in reduction of unbound sum dabigatran concentrations to or below the LLOQ. The effect of idarucizumab on unbound sum dabigatran concentrations was dose-dependent over doses evaluated in this study (1g, 2g and 4g). When an at least equimolar dose of idarucizumab (≥2 g) was administered, gMean unbound sum dabigatran concentrations remained below 10 ng/mL over the entire observation period of 72 h.

In line with the reduction in concentration of unbound sum dabigatran, administration of ≥2 g idarucizumab resulted in immediate,[8] complete,[9] and sustained[10] reversal of dabigatran anticoagulation based on dTT and aPTT. Specifically, administration of:

- 1 g idarucizumab resulted in immediate and complete reversal with subsequent partial return of the dabigatran anticoagulant effect starting between 30 min to 2 h after the end of the infusion as determined by dTT, ECT, aPTT and TT;
- 2 g idarucizumab (that is, the dose calculated to be approximately equimolar to total dabigatran body load) resulted in immediate, complete, and sustained reversal with the clotting assays dTT and aPTT, while the mean ECT and TT values were slightly above the ULN from 6 to 16 h and 2 to 24 h after end of the idarucizumab infusion, respectively.
- 4 g idarucizumab resulted in immediate, complete and sustained reversal with dTT, ECT and aPTT; TT values were slightly above the ULN from 12 to 24 h after end of the idarucizumab infusion
- 5 g + 2.5 g idarucizumab resulted in immediate, complete, and sustained reversal with dTT, ECT, aPTT, and TT.

The main objective of the Phase Ib, randomised, double blind, placebo controlled, two way, crossover Study 1321.2 was to investigate safety, tolerability, PKs, and PDs of idarucizumab (1g, 2.5g and 5g single dose infusion) and to establish the idarucizumab dose(s) effective to reverse the dabigatran induced prolongation of the blood coagulation time in populations resembling the target patient population with respect to age and renal function.

After the end of infusion of all idarucizumab doses and in all populations unbound sum dabigatran plasma concentrations dropped to or below the LLOQ of 1 ng/mL concomitantly with abolished or nearly abolished dabigatran anticoagulation activity. The duration of the effect of idarucizumab on unbound sum dabigatran concentrations increased with dose. When higher idarucizumab doses (2.5 g or 5 g) were infused, gMean concentrations of unbound sum dabigatran remained below 11 ng/mL for the entire observation periods.

Complete reversal of individual dabigatran induced clotting time prolongation within 10 min after end of idarucizumab infusion was observed for all subjects of all dose groups for the clotting parameters dTT and ECT (primary analysis), as well as for aPTT and TT. Placebo infusion had no effect on the clotting parameters. Duration of reversal after idarucizumab infusion was dependent on the idarucizumab dose. Infusion of a total dose of 5 g idarucizumab resulted in sustained reversal of dabigatran induced clotting time prolongation over the entire observation period in healthy subjects (45-64 years) and healthy elderly (65-80 years) as well as subjects with mild renal impairment. When

[8] Timing of the reversal: Reversal of dabigatran induced anti-coagulation occurred directly at theend of idarucizumab infusion.
[9] Magnitude of the reversal: Return of the mean coagulation time of a specific dose group to below the respective ULN.
[10] Durability of the reversal: mean coagulation times of the respective assay remain below ULN during the entire respective observation period. The term 'sustained for x h' was used if effect was less persistent.

administered to subjects with moderate renal impairment, the total dose of 5 g was split into 2 times 2.5 g idarucizumab administered 1 h apart. Immediate, complete and sustained (in between infusions) reversal was observed after the first infusion of 2.5 g.

> *Comments: PD results from study 1321.2 confirm that 5 g idarucizumab is an efficacious dose that reverses dabigatran's anticoagulant activity at exposures in healthy subjects, elderly and subjects with mild or moderate renal impairment matching median exposures observed in patients with atrial fibrillation after 150 mg dabigatran etexilate twice daily dosing.*

In the Phase I, randomised, double blind within dose groups, placebo controlled, single centre Study 1321.5 , single doses of idarucizumab and multiple doses of dabigatran etexilate (Part 2,only) were administered to Japanese young healthy male volunteers. Part 1 (n = 32) and Part 2 (n = 48) had a single rising dose design. The following doses of idarucizumab were administered: Part 1: 1, 2 and 4 g administered as 5 min infusion and 8 g administered as 1 h infusion; Part 2: 1, 2 and 4 g; as well as 2.5 g followed by 2.5 g 15 min later; all administered as 5 min infusion at steady state of a 220 mg dabigatran etexilate bid dosing regimen.

During idarucizumab infusion, a rapid and substantial decline of unbound sum dabigatran concentrations to at least the LLOQ (1 ng/mL) was observed. The duration of the effect of idarucizumab on unbound sum dabigatran concentrations increased with dose, whereby gMean concentrations of unbound sum dabigatran remained below 15 ng/mL after infusion of 2 g idarucizumab and below 4 ng/mL after infusion of higher idarucizumab doses.

In Part 2 of this study, dabigatran etexilate administration consistently prolonged clotting times of all clotting parameters in the absence of idarucizumab. Administration of:

- 1 g idarucizumab resulted in immediate and complete reversal as determined by dTT, ECT, aPTT and TT. By 1 h after end of infusion, all clotting parameters showed a partial return of the dabigatran anticoagulant effect.
- 2 g idarucizumab resulted in immediate and complete reversal as determined by dTT, ECT, aPTT and TT. By 2 h after end of infusion, all clotting parameters showed a partial return of the dabigatran anticoagulant effect.
- 4 g and 2.5 + 2.5 g idarucizumab resulted in immediate, complete, and sustained reversal with dTT, ECT and aPTT. For TT, a partial return of dabigatran anticoagulation was observed between 24 to 48 h (4 g idarucizumab) and at 48 h (2.5 + 2.5 g idarucizumab) after infusion.

The selection of the clinical dose for patients and the demonstration of dose-response was based on biomarker response to different doses of idarucizumab and the concomitant reduction of the unbound sum dabigatran. PK/PD modelling was used to further substantiate dosing considerations. Clinical outcome data were not used in the estimation of the dosing. The calculation of the required dose of idarucizumab is based on a 1:1 stoichiometry of the binding of idarucizumab to dabigatran and the calculated total body load of dabigatran, reflected by the plasma concentrations and estimated volume of distribution. The target clinical dose of 5 g idarucizumab was selected based on the most extreme dabigatran concentrations seen in the RE-LY subgroup with high concentrations, e.g. 99th percentile of concentrations observed in subjects with moderate renal dysfunction based on a population pharmacokinetic model of data from this study and the range of observed trough concentrations ($C_{pre,ss}$) from that study (U09-3249-02). The 99th percentiles of trough and peak concentrations in patients with moderate renal failure were 543 and 861 ng/mL, respectively. These patients will have the highest dabigatran body loads. This coverage with 5 g idarucizumab is regarded as an overwhelming dose. Lower and higher idarucizumab doses have been tested in the Phase I studies.

Comments: Immediate and complete reversal was observed on the basis of the unbound fraction of sum dabigatran and coagulation parameters of dTT, ECT, TT and aPTT after administration of idarucizumab at steady state of dabigatran in all dose groups. The reversal effect was sustained at 4 g and the proposed therapeutic dose of 5 g. Overall, the proposed dose of 5 g (2 x 2.5 g) idarucizumab is appropriate and is being tested in the ongoing Phase III Study 1321.3 in the target patient population.

Efficacy

Studies providing efficacy data

Study 1321.3 was a Phase III, open label, uncontrolled, case series, multicentre study of the reversal of the anticoagulant effects of dabigatran by IV administration of 5.0 g idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures. RE-VERSE AD trial (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran). It is planned to treat approximately 200 to 300 patients with a total dose of 5 g (two 2.5 g vials) of idarucizumab.

Evaluator's conclusions on efficacy

Efficacy of idarucizumab for the proposed indication:

When rapid reversal of the anticoagulant effects of dabigatran is required:

- *for emergency surgery/urgent procedures;*
- *in life-threatening or uncontrolled bleeding*

was assessed, based on the reversal of dabigatran induced anticoagulation as measured by biomarker tests and the level of unbound sum dabigatran.

The selection of the clinical dose for patients and the demonstration of dose-response are based on biomarker response to different doses of idarucizumab and the concomitant reduction of the unbound sum dabigatran. PK/PD modelling was used to further substantiate dosing considerations. Clinical outcome data were not used in the estimation of the dosing. The recommended dose for patients is 5 g idarucizumab.

Comments: Overall, the combined analysis of the three Phase 1 studies supports the proposed total dose of 5 g. It provides evidence that idarucizumab administered at doses of 2.5 g or higher achieves complete reversal in 100% of subjects within about 5 to 6 min after start of infusion. The effect was durable with a median duration of reversal of 72 h. The reversal of anticoagulant effect based on biomarkers was substantiated by pharmacokinetic observations of low plasma levels of unbound sum dabigatran. The assay of unbound sum dabigatran provides an important, independent verification of reversal in addition to the coagulation assays. For example, the sub-therapeutic dose of 1g idarucizumab, after initial complete reversal, shows a rise in unbound sum dabigatran in parallel with a partial return of anticoagulant effect

In the ongoing Phase III Study 1321.3 (RE-VERSE AD), clinical data were available for 123 patients and central laboratory data for assessment of efficacy were available for 90 patients: 51 patients in Group A (bleeding) and 49 patients in Group B (surgery). Efficacy assessment in this study is based primarily on changes in clotting tests after administration of idarucizumab. Each patient served as his own control so an extent of reversibility could be calculated. Verification that changes in clotting tests reflected the

binding and inactivation of dabigatran was accomplished by simultaneous HPLC/MS measurement of unbound sum dabigatran in the same samples. Clinical outcomes such as time to cessation of bleeding, level of haemostasis during surgery, thrombotic events and deaths were also recorded.

In a patient population treated with dabigatran who may need emergency surgery or treatment for uncontrolled bleeding, idarucizumab achieved a median maximum reversal of the anticoagulant effect of dabigatran within the first 4 h of 100%. Complete reversal of the clotting tests was achieved within minutes and the reversal was sustained in approximately 80% of the patients for 24 h. This was confirmed by the fact that unbound dabigatran decreased to below the lower limit of quantitation in parallel with the reduction in clotting. Even in the subset of patients where clotting tests were above the ULN at 12 or 24 h, the reductions in anticoagulant effect were still substantial. These findings confirm that 5 g of idarucizumab represents an overwhelming dose which is sufficient to reverse the anticoagulant effect of dabigatran in almost all patients. This reversal of elevated anticoagulation tests in dabigatran treated patients is a surrogate for clinical efficacy.

A clinical benefit of this reversal depends on the individual patient situation. In this interim analysis, it was difficult to objectively determine the efficacy in stopping bleeding because the bleeds were frequently not visible and difficult to assess, for example, in the case of ICH, some gastrointestinal bleeds or retroperitoneal bleeds. Cessation was subjective and based upon whatever the investigator could visualise or measure. Despite these limitations, bleeding did stop in 44 of 48 evaluable patients within 72 h and the median time to cessation of bleeding was 9.8 h. In the case of emergency surgery, 33 out of 36 evaluable patients had normal haemostasis during surgery. The very short time between treatment with idarucizumab and start of surgery (median 1.7 h) also allowed rapid surgical/procedural intervention. However, in this single cohort study there is no control group so any conclusions based solely on clinical outcomes are limited at best.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

Study 1321.3 was the only Phase III study conducted in the target patient population.

The following safety data was collected in the Phase III study:

- General adverse events (AEs): All AEs occurring before infusion of the first vial idarucizumab were assigned to the screening period. All AEs recorded after the first vial of idarucizumab and until 5 days after the last dose of idarucizumab were assigned to the treatment period. All AEs occurring thereafter until the cut-off date were assigned to the post-treatment period. In addition, AEs with an onset date before start of the trial treatment but with worsening in intensity during the treatment were also assigned to the treatment period. Treatment-emergent AEs are presented for the treatment period (including a washout period of 5 days after last administration of study medication) and the post-treatment period (starting 6 days after last administration of study medication).

Worsening of the underlying disease or of other pre-existing conditions was recorded as an (S)AE in trial 1321.3. Worsening of vital signs, ECG, physical examination and laboratory test results was recorded as an (S)AE, if they were judged clinically relevant by the investigator. Hepatic injury was defined as pre-specified significant AE. For patients

with normal liver function at baseline, this was defined as an elevation of AST and/or LT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample. For patients with impaired liver function tests at baseline, hepatic injury was defined as follows: An elevation of AST and/or ALT >3x ULN combined with an elevation of total bilirubin >2x ULN measured in the same blood sample if transaminases were within normal range; doubling of transaminases combined with an elevation of total bilirubin >2x ULN measured in the same blood sample if transaminases were >2x ULN at baseline.

Pivotal studies that assessed safety as a primary outcome

None.

Dose-response and non-pivotal efficacy studies

Safety data from the three Phase I studies (1321.1, 1321.2 and 1321.5) was pooled and additional information on the individual studies was provided when appropriate. Safety parameters assessed in the Phase I studies included:

- All AEs with an onset any time following the first dose of study drug were assigned to the preceding treatment received. In the pooled analyses of the 3 Phase I trials, all AEs occurring up to 5 days after the last application of trial medication were assigned to the treatment period. All AEs occurring thereafter were assigned to the post treatment period for the pooled analysis of the 3 Phase I studies. Drug related AEs, deaths/ SAEs, discontinuations due to AE and certain pre-specified AEs. The number of subjects with pre-specified AEs was summarised descriptively for treated subjects based on the individual definitions on trial level.

In trial 1321.1, the following AEs were defined as pre-specified significant AEs: Drop in SpO2 <90%, Increase in body temperature >38°C; Drop of systolic blood pressure <90 mmHg, Increase in resting heart rate >100 bpm; Any symptoms of respiratory distress.

The crossover trial 1321.2 categorised the following AEs as pre-specified significant AEs: Hepatic injury with an elevation of AST and/or ALT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample; Increase in body temperature >38°C; Drop of systolic blood pressure <90 mmHg; Increase in heart rate >100 bpm; Any symptoms of respiratory distress.

In the Japanese trial 1321.5, hepatic injury was defined as pre-specified significant AE for subjects with normal liver function at baseline if they had during the trial an elevation of AST and/or ALT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample.

Patient exposure

In the ongoing Phase III Study 1321.3, all of the 123 patients in the interim analysis (dated June 2015) received the pre-specified 5 g dose of idarucizumab. There were 66 patients in Group A (bleeding) and 57 patients in Group B (surgery). The total planned observation time of this study is 3 months. Of 123 patients in this interim analysis, 32 (26%) are still in follow-up at the time of data cut-off with a minimum of 1 month observation. Sixty-two (50.4%) of the remaining 91 patients completed 3 months observation or did not (n = 29, 23.6%); 29 (23.6%) patients did not complete the 3 months duration due to AEs (n = 24, 19.5%), lack of compliance with the protocol (n = 1, 0.8%), withdrawal of consent (n = 1, 0.8%), or other reasons (n = 3, 2.4%).

The median time between the last dose of dabigatran etexilate and the start of the first vial of idarucizumab was 15.6 h, with a wide range from 1.5 to almost 94 h. Approximately 1/3 of patients took their last dose less than 12 h prior to treatment with idarucizumab, with 37% having the last dose between 12 and 24 h and 26% between 24 and 48 h. The IV

administration of idarucizumab was accomplished either as a spiked vial followed by gravity drip (41.5%) or infusion pump (5.7%), or via a syringe (52.8%). The spiking technique was more frequent in Group A while the syringe was more frequent in Group B. The median time for administration was 5 minutes per vial (range 1-16 minutes), with a median total elapsed time between start of the first vial of idarucizumab until the end of the second vial of 19 minutes (range 5-52 minutes). In addition to the 123 patients in this analysis, there were 2 patients after the cut-off date who received a second 5 g dose within 24 h.

There were 283 treated subjects in the 3 Phase I studies. Trials 1321.1 and 1321.2 were conducted in Belgium at the same clinical site while the single centre study 1321.5 was performed in Japan. Of these 283 treated subjects, 224 subjects were treated with idarucizumab and 105 subjects received placebo (regardless of dabigatran etexilate pretreatment). Study 1321.1 contributed half of the subjects (52.7%) to the treatment group 'Ida/DE+Ida' while similar proportions of subjects from Studies 1321.2 and 1321.5 were treated with Ida/DE+Ida. Overall, 141 of 283 treated subjects received pre-treatment with DE, with a contribution of similar proportions of subjects across studies (each approximately one third). All 46 treated subjects in the crossover trial 1321.2 were pretreated with DE before infusion of idarucizumab or placebo whereas about 30% (1321.1) and 60% (1321.5) of the subjects in the respective study received pretreatment with DE. In the combined Phase I studies, a similar number of subjects were either treated only with idarucizumab (107 subjects) or with DE+Ida (117 subjects). In the pooled Phase I trials, the most frequently applied dose of idarucizumab (Ida/DE+Ida) was in the range of ≥1 g to <2.5 g for 41.1% of all subjects, followed by ≥2.5g to <5 g idarucizumab for 21.0% of subjects. Similar proportions of subjects received 5 g idarucizumab (15.6%) or higher doses of >5 g to 8 g idarucizumab (12.1%), based on all subjects receiving idarucizumab with or without DE pretreatment. Among idarucizumab treated subjects who were pre-treated with DE (DE+Ida), the most frequently applied dose of idarucizumab (DE+Ida) was still in the range of ≥1 g to <2.5 g (42.7%) while the proportions of subjects who received 5 g DE+Ida were higher (29.9%) than for the dose range ≥2.5g to <5 g DE+Ida (19.7%).

The vast majority of subjects received idarucizumab as single dose infusion (DE+Ida: 79.5%, Ida/DE+Ida: 89.3%). Overall, 9 subjects (DE+Ida: 7.7%, Ida/DE+Ida: 4.0%) were treated with 2 single infusions of idarucizumab given 15 min apart and 9 subjects (DE+Ida: 7.7%, Ida/DE+Ida: 4.0%) received 2 single infusion of idarucizumab given 60 min apart. Re-exposure to idarucizumab (2 months after the first dose) occurred in 6 subjects (DE+Ida: 5.1%, Ida/DE+Ida: 2.7%) in trial 1321.2.

Safety issues with the potential for major regulatory impact

Liver toxicity

None.

Haematological toxicity

None.

Serious skin reactions

No serious skin reactions were reported in the clinical studies.

Cardiovascular safety

None.

Unwanted immunological events

Overall, 18 of 224 subjects (8.0%) treated with idarucizumab in the Phase I studies had treatment emergent anti idarucizumab antibody responses. Responses were characterised as weak (that is, low titre, maximum titre = 40) and mostly non-blocking, with an even distribution between transient and possibly persistent responses suggesting that idarucizumab may have a low immunogenic potential.

In studies 1321.1, 1321.2, and 1321.5, pre-existing antibodies with cross-reactivity to idarucizumab were seen in 6.5% to 17.5% of subjects (overall 36/283, 13%). These were generally shown to be non-specific antibodies, with low titres, binding to the C-terminus of the molecule.

The presence of pre-existing anti idarucizumab antibodies did not impact reversal of dabigatran induced prolongation of clotting time for the parameters dTT and ECT.

To assess the potential impact of the anti idarucizumab antibody responses on the efficacy of idarucizumab in a subject who might require another course of idarucizumab treatment, a rough estimation of the amount of anti idarucizumab antibody in circulation and this was compared with the dose of idarucizumab that would be administered. For a titre of 40 (corresponding to roughly 3.3 µg/ml anti drug antibodies [ADA]) and 3000 mL plasma volume of a 70 kg person, the amount of anti idarucizumab antibody in circulation calculates to be roughly 10 mg. For the proposed 5 g therapeutic dose of idarucizumab (resulting in peaks of ~20,000 nmol/L), it is clear that the dose is overwhelming in comparison to the estimated maximum concentration of treatment emergent anti idarucizumab antibodies observed to date. Therefore, it is concluded that the impact of anti idarucizumab antibody responses on the efficacy of idarucizumab should be minimal in subjects who may require additional courses of treatment.

In all 3 Phase I studies, antibody formation against idarucizumab and dabigatran was analysed throughout the study including a 3 month follow-up period. An antibody response was defined as treatment emergent in 2 cases. Either the subject showed no positive titre at baseline or a positive titre at post treatment visits. Alternatively, the subject had a positive titre at baseline and the titre increased at post treatment visits relative to the titres determined at earlier time points. No apparent correlation of antibody development to frequency of AEs was observed in any of the 3 Phase I studies.

In the Phase III Study 1321.3, data for ADAs against idarucizumab are available for 47 patients with a pre-dose sample and at least one post dose sample. There were 2 patients with baseline, non-specific ADAs, both of whom had persisting ADAs at 30 days but the binding is not at the variable site. One more patient had a treatment emergent ADA at 30 days, possibly of mixed specificity. These data are very limited but indicate a low level of immunogenicity for idarucizumab, consistent with the levels of immunogenicity identified in the healthy volunteer population from Phase I.

Post marketing data

Post marketing data are not available for idarucizumab as idarucizumab is not yet marketed.

Evaluator's conclusions on safety

In the three Phase I studies in volunteers, 283 subjects were studied, with 224 receiving at least one dose of idarucizumab. Dosing ranged between 20 mg and 8 g. Most of the doses were at least 1 g, with only 23 subjects receiving less than 1 g. Sixty-two subjects received doses of 5 g or more, with 35 subjects receiving the target clinical dose of 5 g. There were no SAEs in idarucizumab treated subjects, no discontinuations due to AEs, no severe AEs, and, importantly, no dose related AEs or drug reactions. There were no AEs associated

with idarucizumab more than with placebo or other comparison groups such as treatment with DE alone. The most common events in subjects treated with idarucizumab were headache (5.4%), skin irritation (2.7%), dizziness (2.2%) and back pain (1.8%). The AE profile in volunteers did not suggest any worsening renal function. Overall, 18 of 224 subjects (8.0%) treated with idarucizumab in the Phase I studies had treatment emergent anti-idarucizumab antibody responses. Responses were characterised as weak (that is, low titre, maximum titre = 40) and mostly non blocking, with an even distribution between transient and possibly persistent responses suggesting that idarucizumab may have a low immunogenic potential.

Interim analysis from the ongoing idarucizumab Study 1321.3 (RE-VERSE AD), provided safety data for 123 patients There were 26 deaths in the study, 13 each in bleeding and surgical patients, reflecting the life threatening nature of the events that qualified them for treatment.. There were 5 patients with thrombotic events during the study but only one of these occurred within 72 h of treatment and none of the patients were on antithrombotic therapy at the time of the event. One of these patients had an ischemic stroke 24 days after treatment and died 2 days later. The other SAEs in the study did not appear to be related to treatment.

The low immunogenicity of idarucizumab observed in Phase I subjects was confirmed in this interim analysis, although the subset was small (data on ADAs to idarucizumab was only available for 47 patients). There were no clear signals of any hypersensitivity reaction.

Overall, the safety in this open label patient cohort was good especially considering the severity of target patient population: (severe bleeding/need for surgery/ invasive procedure). However, interpretation was limited by lack of comparator group.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Praxbind in the proposed usage are:

- Idarucizumab is a humanised monoclonal 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.
- 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.
- Idarucizumab is specific reversal agent for only dabigatran and does not reverse effects of other anticoagulants.
- Idarucizumab has no prothrombotic effect.
- The reversal of the anticoagulant effects of dabigatran by idarucizumab has been demonstrated in 283 healthy volunteers (in 3 Phase I studies). Supportive evidence was provided by interim results from an ongoing Phase III, open label, uncontrolled, case cohort study in 123 patients, with uncontrolled or life threatening bleeding or those requiring emergency surgery/procedures when rapid reversal is required.
- No major safety concerns in a target population of elderly patients with a high frequency of co-morbidities who present at the hospital with a severe or life threatening bleed or a need for emergency surgery/intervention.

First round assessment of risks

The risks of Praxbind in the proposed usage are:

- Risk of thromboembolic events
- Hypersensitivity
- Immunogenicity
- Lack of data on clinical outcomes although it is accepted that it would be difficult to conduct controlled clinical trials in this target population.

First round assessment of benefit-risk balance

A small fraction of patients who are treated with DE and who have co-morbidities may require emergency surgery or other invasive procedures related to those co-morbidities, for example, cardiac catheterisation for a patient with acute coronary syndrome, surgery for a patient with acute appendicitis or major trauma without overt bleeding on presentation. Currently, there is no antidote available to reverse the anticoagulant effect of DE and the acute management of serious bleeding in patients on dabigatran etexilate, including life-threatening bleeds, is limited to supportive care, administration of blood or blood products and, in suitable patients, consideration of haemodialysis to remove the drug.[11] Similarly, there are no other alternatives for the management of dabigatran associated peri-operative bleeds.

Idarucizumab directly, rapidly and specifically neutralises dabigatran's anticoagulant effect due to its very high affinity for dabigatran (Kd = 2.1pM). This affinity is approximately 300-fold higher than the affinity of dabigatran for thrombin (Kd = 0.7 nM). This high affinity for dabigatran means any unbound dabigatran will preferentially bind to idarucizumab. In dynamic equilibrium, any thrombin-bound dabigatran (or other plasma protein bound dabigatran) will equilibrate with unbound dabigatran and rapidly thereafter be bound by any free idarucizumab. Idarucizumab itself has no known pharmacologic effect and preclinical data have shown that it does not bind to factors in the coagulation cascade or other antithrombotics.

The reversal of the anticoagulant effects of dabigatran by idarucizumab, was demonstrated in volunteers, and the effect of the antidote in patients with uncontrolled or life-threatening bleeding or those requiring emergency surgery/procedures when rapid reversal is required is being evaluated in an ongoing study (1321.3) with interim data in 123 patients available at time of submission of current dossier. This was established using several different coagulation tests and corroborated by simultaneously measuring the disappearance of unbound sum dabigatran. An immediate, complete and sustained effect was demonstrated in healthy volunteers, in the elderly, in the renally impaired and in patients with life threatening or urgent conditions that required immediate intervention. This reversal was also demonstrated to be dose dependent and dependent on the amount of dabigatran in the patient. A dose of 5 g of idarucizumab was calculated to be sufficient for full reversal of dabigatran anticoagulant effect in 99% of patients, based on dabigatran plasma concentrations observed in the RE-LY trial. A massive amount of dabigatran, as could occur in cases of Pradaxa overdosage, may also be reversed by the proposed clinical dose of 5 g. However, plasma concentrations in excess of e.g.800 ng/mL may result in partial reversal. The complete dose of 5 g is administered intravenously, as two consecutive infusions over 5 to 10 minutes each or as a bolus injection. Local coagulation

[11] Weitz JI, et al. Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation 126: 2428-32 (2012). Majeed A, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation* 128: 2325-32 (2013).

tests, for example, aPTT, dTT, pre and post treatment, may help the treating physician determine whether reversal of dabigatran has occurred.

The reversal of elevated anticoagulation tests in dabigatran treated patients is a surrogate for clinical efficacy. Together with a direct assay demonstrating the removal of "active" dabigatran (unbound sum dabigatran) from the plasma, these data document the pharmacologic effect of idarucizumab in the target population.

While improved clinical outcomes of, for example, reduction or stoppage of bleeding, or decrease in bleeding-associated mortality in a controlled clinical trial would be preferred, ethical and logistic constraints, as well as the need for an extremely large sample size, mean such a trial would take years to complete if it could be done at all. Even after over 50 years of use of warfarin and congeners, there are no clinical outcomes data showing clinical benefit or mortality reduction in bleeding patients on warfarin with administration of Vitamin K or fresh frozen plasma (FFP). In this context, demonstration of pharmacologic reversal of dabigatran in the target patient population, coupled with data in the same patients showing that unbound sum dabigatran levels were reduced at the same time was the proposed clinical development approach for idarucizumab.

The reversal of coagulation test values and reduced levels of unbound sum dabigatran reliably demonstrate reversal of dabigatran induced anticoagulation. Idarucizumab addresses the potential clinical need for an agent to rapidly reverse the anticoagulant effects of dabigatran in case of emergency surgery or life threatening or uncontrolled bleeding associated with dabigatran.

Idarucizumab is not intended for use in patients with minor bleeding or other bleeding where standard supportive care is sufficient. It is expected that usage of this drug would be confined to emergency departments or other critical care facilities.

Idarucizumab had an excellent safety profile in healthy volunteers with no SAEs, no discontinuations due to AEs, no severe AEs, and no dose related AEs or drug reactions. Similarly, in the 123 patients (included in the interim analysis of Phase III study 1321.3), AEs were common but appeared to be unrelated to treatment. Nine of the 26 deaths were either due to the events at presentation or later in the trial due to co-morbidities. The mortality rate was not unexpected in a high risk population with life threatening events. Though two patients developed thrombotic events, these occurred 9 and 13 days after treatment with idarucizumab and in the absence of any antithrombotic treatment. Thus, there was no indication of a pro-thrombotic effect, consistent with evaluations in volunteers and with the preclinical data. There was no evidence of worsening renal function when this drug is given to patients with renal impairment and full efficacy is maintained. Other blood products may be administered as required.

Overall, the ability to safely reverse the anticoagulant effect of dabigatran in patients who require rapid reversal could improve the surgical risk of patients requiring emergency surgery, improve the management of serious bleeding events and further increase the overall safety profile of anticoagulation therapy with dabigatran.

The benefit-risk balance of Praxbind, given the proposed usage, is favourable.

First round recommendation regarding authorisation

It is recommended that approval be granted for Praxbind (idarucizumab) for the proposed indication:

> *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.*

However, approval is subject to the following:

- incorporation of suggested changes to the proposed PI
- continued approval for this indication may be contingent upon the results of the ongoing cohort case series study (1321.3) and results should be provided for evaluation on completion of this study.
- an adequate response to questions below.

Clinical questions

Pharmacokinetics

None.

Pharmacodynamics

None.

Efficacy

Question 1

A 4 month safety update summarises safety and efficacy data from this ongoing study and provides data in 123 patients. However, the cover letter, clinical overview and clinical summary of efficacy in the current submission only summarise data in 26 patients from Study 1321.3. Can the sponsor please provide clarification on why data from the 123 patients was not included in the summary of efficacy or overview especially considering fact that both FDA and EMA mention data from 123 patients in their approval statements and labelling?

Question 2

Table 2.1.1:2 of the Clinical summary of efficacy mentions dose groups as Part 1 and Part 2 (see below: shown as Table 4).

Table 4. Comparison of mean $AUEC_{above,2-12}$ ratio post-Ida/pre-Ida for the coagulation markers dTT, ECT, aPTT and TT.

	$AUEC_{above,2-12}$ [h] ratio Day 4/Day 3			
Dose group	dTT	ECT	aPTT	TT
Part 1 *(5 min idarucizumab infusion)*				
DE+plc	1.01	1.04	1.28	1.08
DE+1 g Ida	0.26	0.28	0.46	0.32
DE+2 g Ida	0.06	0.07	0.14	0.06
DE+4 g Ida	0.02	0.03	0.07	0.00
Part 2 *(5 min idarucizumab infusion)*				
DE+2 doses plc	1.02	1.22	1.68	1.11
DE+5 g+2.5 g Ida	0.01	0.02	0.03	0.00

Plc=placebo, Ida=idarucizumab, DE=dabigatran etexilate
Ratios of $AUEC_{above,2-12}$ were calculated based on the effect ratio (observed value divided by baseline value) whereby only the area under the effect curve above 1 was considered.

There is an error in this table as Part 1 did not involve administration of dabigatran and it should actually read Part 2 and Part 3. Can the sponsor provide clarification on this?

Safety

None.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Praxbind in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Praxbind in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit-risk balance of Praxbind in the proposed usage is unchanged from that identified in the first round evaluation.

Second round recommendation regarding authorisation

It is recommended that approval be granted for Praxbind (idarucizumab) for the proposed indication:

> *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.*

Continued approval for this indication may be contingent upon the results of an ongoing cohort case series study.

V. Population pharmacokinetics

Rationale

This evaluation reviews a population PK analysis of idarucizumab and its interaction with dabigatran and effect on the PK-PD of dabigatran on coagulation biomarkers in three Phase I studies. The report is entitled "Idarucizumab and dabigatran population pharmacokinetics and dabigatran exposure-response relationships in healthy subjects".

The report was evaluated to determine the validity of the analysis methods and results and their clinical implications.

Evaluation of analysis conducted

Analysis conducted

The analyses conducted included a population PK analysis to characterise the disposition of and interaction between idarucizumab and dabigatran and PK/PD analyses to characterise the effect of dabigatran on coagulation biomarkers in three Phase I studies, 1321.1, 1321.2 and 1321.5.

Analyses were conducted by the sponsor.

Evaluation of analysis conducted

Base and final population PK models were evaluated. Analyses were run using NONMEM v7.3, whereas v7.2 was used to generate the PK results provided by the sponsor.

The PK control files for the base and final PK models, respectively, were run after simplification of the variance-covariance matrix to estimate only the diagonal elements. The results were compared with the sponsor's PK output files. Parameter estimation was successfully performed using the iterative two stage method and the Expectation Maximization using Monte Carlo importance sampling. However, implementation of the Stochastic Approximation Expectation Method failed to run successfully. Nevertheless, PK parameter estimates using the methods implemented were consistent with those reported by the sponsor and were deemed sufficiently similar to validate the sponsor's results.

Results summary

In summary, detailed descriptions of the analysis data sets, PK modelling results and PK/PD modelling results were presented in a logical manner using accepted model building and model evaluation techniques. However, there were some omissions and inconsistencies that hindered interpretation of the results:

- a complete description of the PK data set and exclusions and more granularity in the development of the structural PK model (as recorded in the run log) would have been useful,
- trends in goodness of fit plots were shown using smoothing functions for the PK model but not for the PK/PD models,
- correlations among covariates were illustrated using scatterplots with smoothing functions and correlation coefficients for the PK/PD analysis but not the PK analysis,
- in the PK/PD model evaluation but not the PK model evaluation, sensitivity analyses were conducted to explore the impact of outliers on parameter estimation,
- handling of BLQ idarucizumab plasma concentrations and their impact on PK parameter estimation was not discussed anywhere in the report,
- sensitivity analysis to explore the effect of outliers on parameter estimation was conducted for the PK/PD model evaluation but not for the PK model,
- critical evaluation of the VPC plots to address model deficiencies was lacking.

Application of the models to perform simulations was appropriately justified and presented to address their intended purpose. Overall, the population PK and PK/PD

models provided acceptable descriptions of the data and the modelling and simulation results were presented in accordance with EMA guidelines.

Discussion and conclusion

Discussion and conclusions drawn of the PK/PD report focussed on the principal findings of the modelling and simulation analyses and their clinical implications. Points of discussion and a critique are as follows:

Population PK

- Idarucizumab PK was described. The central (Vc) and steady state (Vss) volumes were estimated to be 3.25 L and 9.24 L for a 75 kg subject, suggesting that idarucizumab is confined to extracellular fluid. It was stated that idarucizumab PK was linear and not altered when bound to dabigatran. However, these assumptions were based on general goodness of fit of the linear model to the data and were not formally tested.
- Idarucizumab clearance (CL) was reduced in subjects with renal impairment while Vc varied with body weight. An effect of Japanese race on idarucizumab CL was deemed to be not clinically relevant.
- Ultrafiltration was used to exclude quantitation of idarucizumab-bound dabigatran from quantitation of sum dabigatran. However, it also excluded plasma protein bound dabigatran. Consequently, unbound sum dabigatran was quantified and sum dabigatran was derived using the population PK model.
- Both renal function and age were included as covariates on dabigatran CL/F.
- Contrary to the statement that age was an influential covariate, it was included in the model based on previous experience but was not statistically significant nor clinically relevant (8% change in CL/F over 20-80 years age range).
- Previously, the relationship between renal function and dabigatran CL/F was characterised using a saturable (Emax) relationship. This model was not tested in the analysis because of the small number of subjects with renal impairment in the analysis data set. Instead, a power model described the decrease in dabigatran CL/F with greater renal impairment.
- It was noted that the rate and extent of dabigatran redistribution after idarucizumab administration were overestimated in subjects with renal impairment. Inclusion of an additional effect of renal impairment on CL/F and Q/F did not substantially improve the model and warrants further evaluation.
- Dabigatran CL/F was increased by 16% in Japanese subjects relative to Caucasian subjects with normal renal function. The difference was not deemed clinically relevant in light of previously published results.[12]
- It was noted that previous dabigatran PK models have estimated a large Vc/F relative to Vss/F (Vc/F = 756 L and Vss/F = 1101 L) for an 80 kg subject. However, in the present PK model, Vc/F and Vss/F were estimated to be 278 L and 960 L, respectively, suggesting that the majority of the drug was distributed peripherally not centrally. These estimates derived from the interplay of the amount of drug in the periphery, distributional rate constants and the relative sizes of the central and peripheral compartments influencing dabigatran redistribution after idarucizumab

[12] Haertter S, et al. Pharmacokinetics and pharmacodynamics in Japanese and Caucasian subjects after oral administration of dabigatran etexilate. *Thromb Haemost.* 107: 260-269 (2012).

administration and this perturbation of the system may have more accurately reflected dabigatran disposition.

Population PK/PD models

- Although not referenced, it was noted that model predicted sum dabigatran: coagulation biomarker PK/PD relationships were similar to those previously reported. The implications are two-fold: first, there was no clinically relevant effect of idarucizumab on PK/PD relationships (notwithstanding the PK effect of binding dabigatran to render it unavailable in plasma to have an anticoagulant effect). Second, it permits extrapolation of idarucizumab induced reversal of dabigatran anticoagulant effects to the patient population.
- For models in which unbound sum dabigatran was the independent variable, the slope was reduced by approximately 30% corresponding to 30% lower unbound sum dabigatran concentrations compared to sum dabigatran concentrations.
- For each of the coagulation biomarkers, there was a significant effect of Japanese race. For the most part, the effect of race could be exchanged for an effect of Study 1321.5 in addition to other study effects in Studies 1321.1 and 1321.2. It was discussed that the effect of race was a surrogate for study effects attributed to bioanalytical differences due perhaps to lot to lot variations in coagulation biomarker assays. The effect of Japanese race remains to be further examined in a patient population (Phase II/III).
- Age, body weight and idarucizumab administration were identified as significant predictors IIV in the PK/PD analyses. However the effect sizes were small and as such could be considered to be clinically irrelevant in the Phase I population evaluated.

Simulations

- Simulations demonstrated complete reversal of coagulation in > 96% Caucasian and Japanese patients (75 years of age) across a broad range of renal function (CrCL = 40-120 mL/min) following single doses of 1 to 5 g or 2.5 + 2.5 g of idarucizumab. There was no apparent difference in response to a single 5 g dose or two 2.5 g infusions separated by 15 minutes.
- Idarucizumab was effective over a broad range of renal function. Since CL of idarucizumab and CL/F of dabigatran were both reduced in renal impairment, there may be increased opportunity for binding and therefore efficacy was predicted to be maintained despite renal impairment.

The stated conclusions clearly summarised the key points made in the discussion. These were succinct and appropriately summarised the main findings of the study.

Summary and implications

Summary

Analyses conducted to characterise the population PK of idarucizumab, its binding interaction with dabigatran and extrinsic factors that may influence idarucizumab PK. In addition, dabigatran's effect on coagulation biomarkers and the possible influences of extrinsic and treatment related factors were investigated using a population analysis approach. The methods used were generally appropriate and adequate for their purpose.

On the basis of this evaluation, it was concluded:

- A population PK model was developed to describe the disposition of idarucizumab and dabigatran when administered alone and in combination in healthy subjects. The base and final PK models were verified. Effects of significant covariates identified in the analysis, including age, body weight, renal function and race, remain to be validated in a patient population.
- Unbound dabigatran plasma concentrations were substantially decreased in the presence of idarucizumab due to the formation of an idarucizumab-dabigatran complex. While the model captured the binding interaction, there was some misspecification of the model during the dabigatran redistribution phase that warrants further review of the model. Dabigatran redistribution from the peripheral to the central compartment was attenuated with increasing doses of idarucizumab.
- The primary demographic covariate influencing clearance of both drugs was renal function. As a result, exposures to both idarucizumab and dabigatran may be expected to be increased in renal impairment with increased opportunity for binding. Consequently, idarucizumab efficacy may be expected to be maintained in renal impairment as shown in simulations over a CrCL range of 40-120 mL/min.
- Notwithstanding the PK effect of binding dabigatran to render it unavailable in plasma to have an anticoagulant effect, the underlying relationship between dabigatran exposure and anticoagulation was unaffected by idarucizumab coadministration. The clinical relevance of the effect of Japanese race on these relationships remains to be further examined in a patient population (Phase II/III).
- Rapid and complete reversal of coagulation was shown to occur in 100% of simulated subjects (40 y and 75 years old Japanese (60 kg) and Caucasian (80 kg), CrCL = 40-120 mL/min) after a 5 g idarucizumab dose given either as a single infusion or as two 2.5 g infusions 15 min apart. The impact of extremes of body weight by itself and in the presence of renal impairment warrants investigation as both factors significantly influenced idarucizumab disposition.

Implications

The PK and PK/PD analyses conducted included 244 and 189 healthy subjects, respectively, from 3 Phase I trials. Modelling and simulation results support the administration of 5 g idarucizumab as a single infusion or as two 2.5 g infusions 15 min apart to reverse the anticoagulant effects of steady-state dabigatran (administered as 150 mg or 220 mg BID DE over 4 days). Experience in patients is required to validate the models developed herein using phase 1 data and to provide justification for dosage selection in the clinical setting. Moreover, dose selection must be evaluated in the context of safety data, which was not included in the PK/PD report.

Considerations with regard to the proposed PI are as follows:

- Elderly patients/sex/race and renal impairment
  - Conclusions regarding effects of age, sex, race and renal impairment on idarucizumab exposure based solely on Phase I data are premature and require validation with patient data. On this basis, they should be qualified as preliminary, or removed. Furthermore, based on Phase I data, renal impairment and body weight are both important determinants of idarucizumab exposure and consideration should be given to exposures at the extremes of these covariate ranges, separately and together.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU RMP (version 2.0, dated 19 November 2015, DLP 17 September 2015) with Australian Specific Annex (ASA) (version 2.0, dated 4 December 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Ongoing safety concerns.

Ongoing safety concern	
Important identified risks	None
Important potential risks	Immunogenicity Hypersensitivity Thrombotic events Patients with hereditary fructose intolerance
Missing information	Paediatric patients Pregnancy/breast-feeding Re-exposure to idarucizumab

RMP reviewer comment

Use in patients with renal impairment should be included as an item of missing information in the RMP/ASA.

The sufficiency of the summary of safety concerns will also be considered by the Advisory Committee on the Safety of Medicines (ACSOM).

The adequacy of the summary of safety concern is also subject to assessment by the clinical and nonclinical evaluators.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine pharmacovigilance activities are proposed for all safety concerns. The following additional pharmacovigilance activities are also proposed (Table 6).

Table 6. Proposed pharmacovigilance activities.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Trial 1321.3 Phase III case series clinical study (ongoing)	Important potential risks: 'Immunogenicity', 'Hypersensitivity' and 'Thrombotic events'.	To evaluate the reversal of the anticoagulant effects of dabigatran by IV administration of 5g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures.	Final report Q4 2017.
Idarucizumab drug administration surveillance program	No specific safety concerns assigned.	No detail provided	Final report planned for Q1 2019 depending on enrolment and market authorisation status.
Trial 1321.11 Non-interventional paediatric safety study.	Missing information: 'paediatric patients'	To evaluate the safety in potential paediatric patients.	Final report planned for Q1 2019 depending on enrolment and marketing authorisation status.

RMP reviewer comments

A protocol for Trial 1321.3 has been provided as an attachment to the EU RMP.

Little information is given regarding the 'idarucizumab drug administration surveillance program' which is briefly mentioned in the RMP but is not included in the ASA. The sponsor should provide further details of this activity including its objectives as additional pharmacovigilance. Sufficient detail should also be included in a revision to the ASA.

Advice will be sought from the ACSOM as to the adequacy of the pharmacovigilance plan to monitor risks associated with idarucizumab in Australia.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation (that is, product labelling) is sufficient to mitigate the risks associated with idarucizumab. No additional risk minimisation activities are proposed.

RMP reviewer comment

Routine risk minimisation activities may be acceptable as long as the PI and CMI are sufficiently robust.

Advice will be sought from the ACSOM regarding the adequacy of the risk minimisation plan to mitigate risks associated with idarucizumab, particularly given the paucity of international post marketing experience.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

The evaluator's comment has been noted.

Evaluator's comment

N/A

Recommendation #2 in RMP evaluation report

Section 4.2: Given the recent positive opinion in the EU, the sponsor should confirm whether the RMP submitted to Australia is identical to the RMP accepted in the EU. If there have been changes to the RMP as a result of negotiations in the EU, the updated EU RMP reflecting these changes should be submitted with the Section 31 response.

Sponsor response

As a result of negotiations in the EU some details of the RMP have been changed. The updated RMP version 2 dated 19 November 2015 and the corresponding updated ASA are provided with this response.

During the discussion with EMA, the most important change of the EU-RMP was the deletion of the important identified risk "Patients with hereditary fructose intolerance". The reason for the deletion was the fact that under emergency or life-threatening conditions, the benefit-risk ratio in these patients may be positive. Based on this, in the EU-SmPC, no contraindication for patients with hereditary fructose intolerance has been included but a precaution is included in the warning section.

Evaluator's comment

This is acceptable from an RMP perspective.

Recommendation #3 in RMP evaluation report

Use in patients with renal impairment should be included as an item of missing information in the RMP/ASA unless a compelling justification can be provided.

Sponsor response

The sponsor has provided the requested justification (see Section 31 response).

Evaluator's comment

The sponsor's justification not to include 'patients with renal impairment' as an item of missing information is acceptable from an RMP perspective.

Recommendation #4 in RMP evaluation report

Little information is given regarding the 'idarucizumab drug administration surveillance program' which is briefly mentioned in the EU RMP but is not included in the ASA. The sponsor should provide further details of this activity including its objectives as additional pharmacovigilance. Details of this activity should also be included in a revision to the ASA.

Sponsor response

The idarucizumab drug administration surveillance program aims to globally monitor the use of idarucizumab in routine clinical practice including a large proportion of patients receiving idarucizumab. The program will be globally available to all hospital pharmacies where idarucizumab is dispensed depending on market authorisation, country regulations and requirement. The data collected in this surveillance program will be fully anonymised and hospital pharmacy characteristics, basic demographic data as well as basic information on the use of idarucizumab (such as indication of use) will be collected.

Details of the program can be found in the submission in document "Reports of post marketing experience". This document is also attached with this response.

Boehringer Ingelheim is currently assessing the feasibility of implementing this program in Australia. As such, this has not been included in the ASA.

Evaluator's comment

Results of this activity should be communicated to the TGA in the appropriate fashion, as well as in Periodic Safety Update Reports (PSURs).

It is recommended that the surveillance program should be extended to include Australian patients.

Recommendation #5 in RMP evaluation report

From a risk minimisation perspective there is a risk of under dosage given two 2.5 g vials are required to achieve the recommended dose. Given there are no alternative dosage regimens proposed it is unclear why a 5 g vial has not been made available and the sponsor should provide the rationale for the current dosage presentation.

Sponsor response

The sponsor has provided a justification in response to this question (see Section 31 response).

Evaluator's comment

There is an inherent risk of medication error when 2 vials are required to achieve a standard dose. There should be a low threshold for re-examining the risk minimisation plan should reports of medication error occur in the post marketing period.

Recommendation #6 in RMP evaluation report

The ASA briefly mentions "therapeutic area specific educational material". Little detail is provided and it is unclear if the sponsor is proposing this as an additional risk minimisation activity. More detail should be provided with the Section 31 response including draft educational materials if available.

Sponsor response

As stated in the ASA, the sponsor provides therapeutic area specific educational material on an ongoing basis.

As part of our routine new product launch activities and commitment to the quality use of medicines, product specific educational materials will be provided to hospitals that request access to idarucizumab (currently via Special Access Scheme (SAS)). These materials include information on the proper and safe use of the product, identification of appropriate patients and dosage and administration information. They have been developed in close consultation with our local idarucizumab advisory board which is comprised of cardiologists, neurologists, haematologists, anaesthetists, emergency physicians and a hospital Director of Pharmacy. A group of trained medical personnel will be available to provide face-to-face training to hospitals.

A copy of the current educational materials is provided with this response:

- Idarucizumab for dabigatran (Pradaxa) reversal key considerations for clinicians
- Idarucizumab for dabigatran (Pradaxa) reversal SAS reference guide
- Idarucizumab for dabigatran (Pradaxa) reversal clinical in-service presentation slides
- Idarucizumab for dabigatran (Pradaxa) reversal SAS reference chart
- Idarucizumab for dabigatran (Pradaxa) reversal frequently asked questions and answers

Evaluator's comment

Once approved the sponsor should amend the educational materials to reflect the registration of the product and remove references to the SAS which will no longer apply.

The evaluator has no objection to the content of the educational materials.

For completeness the ASA should include information on how and when these materials will be distributed and to whom. The educational materials should also be attached to the ASA as they are considered to be an additional risk minimisation activity.

Recommendation #7 in RMP evaluation report

No assay is currently recommended to titrate or monitor dabigatran's anticoagulant effect in a clinical scenario. This is challenging in the context of an emergency reversal where laboratory confirmation that the reversal has worked would be most useful. There appears to be little guidance in the PI as to how the "reversal" can be confirmed and inclusion of such information in the PI may minimise unnecessary repeat dosing.

Sponsor response

The sponsor has provided a response to this recommendation (see Section 31 response).

Evaluator's comment

As long as a reliable assay is not available to test the anticoagulant effect of dabigatran the determination of whether the idarucizumab reversal has worked or not is ultimately a clinical one based on a number of factors including physical examination and laboratory testing.

The risks associated with incomplete reversal are difficult to mitigate in these circumstances.

Recommendation #8 in RMP evaluation report

'Hypersensitivity to idarucizumab or any of its excipients' should be added as a contraindication and included as routine risk minimisation for the important potential risk 'hypersensitivity'.

Sponsor response

The sponsor proposes not to add 'Hypersensitivity to idarucizumab or any of its excipients' as a contraindication to the Australian PI and idarucizumab RMP for the following reasons:

Patients to be treated with idarucizumab are mostly critically ill and often in an emergency situation. A careful benefit-risk assessment by the treating physician on single patient level may result in a benefit for idarucizumab treatment. In such a situation, a contraindication may prevent a treating physician from the administration of idarucizumab which may put the patient on an increased risk for an unfavourable outcome.

Patients treated with idarucizumab are treated under emergency conditions which would allow treatment of events associated with hypersensitivity accordingly.

BI proposes not to include 'hypersensitivity to idarucizumab or any of its excipients' as a contraindication. Instead, the proposed Australian PI includes the following strong warning statement in the Precautions section:

> *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.*
>
> *The statement above is in line with that in the EU-SmPC section 4.4 Special warnings and precautions for use.*

Evaluator's comment

The sponsor's justification is acceptable from an RMP perspective.

The decision of whether or not to include hypersensitivity as a contraindication is for final determination by the Delegate.

Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 Request has adequately addressed most of the issues identified in the RMP evaluation report.

There are outstanding issues.

Outstanding issues

ASA

The educational materials currently used with SAS use in Australia are considered to be additional risk minimisation activities. It is expected that similar education will continue post approval.

Therefore, it is recommended that the sponsor should amend the educational materials to remove references to the SAS which will no longer apply. Once amended, the draft

materials should be included as an attachment to the ASA. The ASA should also be updated to include further information on the distribution strategy and effectiveness assessment of the educational materials. The amended ASA with the updated materials should be submitted to the Pharmacovigilance and Special Access Branch prior to approval.

Advice from ACSOM

The evaluator sought advice from the ACSOM regarding RMP issues. The ACSOM advice has been considered in reconciling the outstanding RMP issues for this submission.

Comments on the safety specification of the RMP

Clinical evaluation report

The Safety Specification in the draft RMP (version 1) is satisfactory. The safety specifications identified by the sponsor in the RMP are consistent with the adverse events/safety profile from the clinical trial data in the submission.

Nonclinical evaluation report

Results and conclusions drawn from the nonclinical program for idarucizumab detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator.

Key changes to the updated RMP

EU RMP (version 1.0 dated 27 January 2015, Data Lock Point [DLP] 4 September 2014) with an ASA version 1.0 (dated 18 March 2015) has been superseded by:

- EU RMP (version 2.0, dated 19 November 2015, DLP 17 September 2015) with ASA (version 2.0, dated 4 December 2015)

Outstanding RMP issues remain in this advice.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

No wording for the RMP condition can be supplied at this time as outstanding RMP issues remain (see above).

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator had no objection to the registration of idarucizumab. The following was noted during the evaluation of the quality aspects of the submission:

- Idarucizumab is a humanised Fab fragment of the murine IgG1 antibody directed against the thrombin inhibitor dabigatran.
- The predicted molecular mass of idarucizumab is 47,766 Da. It consists of one light chain polypeptide of theoretical average molecular weight of 24,043 Da (reduced) and one heavy chain fragment polypeptide of theoretical average molecular weight of

23,733 Da (reduced). The two chains are linked by a single disulphide bond. The predicted amino acid sequences of the heavy and light chains.

- Idarucizumab binds dabigatran in a concave region at the interface of the variable domains.
- Idarucizumab is produced by expression in Chinese Hamster Ovary cells applying standard mammalian cell culture techniques.
- Purification and formulation of idarucizumab consists of a series of chromatographic steps (affinity, anion and cation exchange chromatography), virus inactivation, virus filtration, concentration and buffer exchange by tangential flow filtration and final filtration through a 0.2 µm filter.
- Idarucizumab drug substance is a colourless to slightly yellow, clear to slightly opalescent solution.
- The formulation contains the excipients acetic acid and 25 nM sodium acetate (for buffering), 220 nM sorbitol and 0.2g/L (0.02 w%) polysorbate. It has a final pH of 5.5 (5.5-5.7), and an osmolality of 270-330 mOsmol/kg.
- The stability data supported a shelf life for the drug product of 24 months when stored at 2-8°C. The final product is not photostable.

Nonclinical

The evaluator had no objections to the registration of idarucizumab. The evaluator considered the qualities of the studies was high and the nonclinical testing strategy was appropriate for the proposed product. The following were noted during the nonclinical evaluation:

- Idarucizumab affinity for dabigatran (Kd 2.1 pM) was > 300 fold higher than the affinity of dabigatran for thrombin (Kd 0.7 nM) at pH 7.4, and at pH ≥ 6 Kd was ≤ 62 pM, suggesting that preferential binding to idarucizumab should take place in the presence of acidaemia.
- Anticoagulant activity of dabigatran and its acyl glucuronidated active metabolites was reversed by idarucizumab in whole blood and plasma and reduced blood loss in animal models.
- Intravenously administered idarucizumab exhibited similar pharmacokinetic parameters in the presence and absence of dabigatran in all species, while total dabigatran plasma levels (including bound and unbound) were increased by idarucizumab. Idarucizumab distribution was confined to the vascular milieu.
- Excretion of idarucizumab was through the urinary route with a small fraction excreted unchanged, while the remainder was through excretion of catabolised protein. Renal impairment increased plasma exposure to both idarucizumab and dabigatran.
- Repeat dose IV toxicity studies of up to 4 weeks in rats and 2 weeks in monkeys found no evidence of systemic toxicity. In the rat, altered haematological and serum chemistry parameters did not correspond to notable post mortem findings. In the monkey, the only adverse findings were from a male from a 2 day dosing study with renal function changes, which did not correspond to treatment related findings of note. Relative exposures attained in the animal studies were low (≥ 6 times the clinical AUC).
- Development of antibodies against idarucizumab was seen in rats and monkeys. There were no adverse findings in animals from the main repeat dose toxicity studies

associated with immunogenic reactions aside from an isolated hypersensitivity reaction in a monkey intermittently dosed with idarucizumab.

- Idarucizumab or its complex with dabigatran did not bind with other endogenous target such as other thrombin substrates (factors V, VIII, XIII, fibrinogen, vWF, PAR-1 peptide or protein C), or plasma or serum albumin and did not cause haemolysis of whole human blood.
- No major organ toxicity was identified and no clinically relevant effects on respiratory, cardiovascular and CNS systems are anticipated.
- The potential genotoxicity, reproductive or developmental toxicity was not tested in animal models but this was considered acceptable given the likely infrequent pattern of use and the likely clinical settings. The evaluator supported the sponsor's proposed Pregnancy Category of B2.
- There was no specific testing in juvenile animals.
- Idarucizumab did not reverse rivaroxaban, apixaban, hirudin, argatroban, heparin or enoxaparin induced anticoagulation and did not exhibit its own pharmacological/prothrombotic activity. It did not affect the activity of antiplatelet agents (ticagrelor and clopidogrel). It did reverse the activity of melagatran (another factor IIa inhibitor, not registered in Australia)
- Haemodilution and volume expanders (for example, 4% hydroxyethyl starch) did not affect dabigatran binding with idarucizumab.

Clinical

The clinical dossier included:

- 3 Phase I studies (Studies 1321.1, 1321.2 and 1321.5) in healthy volunteers
- 1 population pharmacokinetic and pharmacodynamic study
- 1 (ongoing) phase III study (1321.3)
- Integrated summaries of pharmacology, efficacy and safety

Pharmacology

- Three pharmacology studies (Studies 1321.1, 1321.2 and 1321.5) were submitted. These form a large part of the human exposure to idarucizumab. From these studies and the population pharmacokinetic Study PopPK 01-02-05, the PK of idarucizumab and the effects on dabigatran pharmacokinetics were characterised by:
  - Cmax was 25 µmol/L, 28.3 µmol/L, 32.1 µmol/L after 5 g idarucizumab by infusion given to healthy volunteers aged 45-64, healthy volunteers aged 65-80, and subjects with mild renal impairment, respectively. Cmax was 26.5 µmol/L after 2 doses of 2.5 g idarucizumab in subjects with moderate renal impairment.
  - Median Tmax of 6 minutes after a 5 g dose in healthy volunteers
  - $AUC_{0-\infty}$ was 37000 nmol·h/L, 43900 nmol·h/L, and 53100 nmol·h/L after 5g idarucizumab by infusion given to healthy volunteers aged 45-64, healthy volunteers aged 65-80, and subjects with mild renal impairment, respectively. $AUC_{0-\infty}$ was 67900 nmol·h/L after 2 doses of 2.5 g idarucizumab in subjects with moderate renal impairment.
  - Cmax and AUC were dose proportional over the range 20 mg to 8 g.

- Volume of distribution was 6.34 to 8.86 L after a 5 g infusion. The population PK modelled central volume of distribution was 3.3 L and was a function of body weight.
- Clearance was 47.1 mL/min, 39.6 mL/min and 32.8 mL/min after 5 g idarucizumab by infusion given to healthy volunteers aged 45-64, healthy volunteers aged 65-80, and subjects with mild renal impairment, respectively, and 25.7 mL/min after 2 doses of 2.5 g idarucizumab in subjects with moderate renal impairment.
- After IV administration of a 5 g dose 32.12% (gCV 60%) was recovered in the urine in the first 6 h, and <1% in the next 18 h.
- In volunteers aged 45-64 years the initial half-life was 47 minutes (gCV 11.4%).
- The terminal half-life was 10.3 h, 10.8 h, and 9.52 h after 5 g idarucizumab by infusion given to healthy volunteers aged 45-64 years, healthy volunteers aged 65-80 years , and subjects with mild renal impairment, respectively, and 10.1 h after 2 doses of 2.5 g idarucizumab in subjects with moderate renal impairment.
- A dose dependent increase in low-molecular weight proteins and urine proteins was seen immediately after dosing that peaked at 4 h then returned to normal in almost all cases within 12-24 h. This is thought to be the result of catabolism of idarucizumab protein in the kidney and saturation of tubular uptake processes for the resorption of small (≤ 70 kDa) proteins from the urine filtrate, rather than acute tubular injury.
- A small increased (up to 1.2 fold) in idarucizumab PK parameters was observed when idarucizumab was administered with steady state dabigatran.
- Doses of 1 g, 2 g, 4 g, and 5 g idarucizumab all reduced unbound sum dabigatran concentrations to or below the LLOQ immediately after IV infusion and the decrease was dose-dependent. The decrease was accompanied by an idarucizumab dose-dependent increase in sum dabigatran.
- Idarucizumab transiently reduced the urinary excretion of dabigatran.
- Re-exposure to dabigatran 24 h after administration of idarucizumab or placebo in healthy subjects aged 45-64 years showed similar trough and peak dTT, ECT, aPTT and TT ratio to baseline pre and post idarucizumab.
- Population PK analysis showed the PK of idarucizumab was best described by a three compartmental fixed effects. Idarucizumab had a steady stated Vd of 9.2L, the model estimate for clearance was 2.3L and the terminal half-life was approximately 12 hours. Clearance was a function of renal function, but not age, sex, and body weight. Weight adjusted clearance was similar in Japanese and white subjects. The size of the central compartment varied with body weight.

- The pharmacodynamic effects of idarucizumab from the Phase I studies are:
  - Idarucizumab had no direct effect on dTT, ECT, TT, aPTT, or activated clotting time (ACT) suggesting there was no effect on the coagulation cascade.
  - The mean and individual endogenous thrombin potential (ETP) profiles, fibrinopeptide A and coagulation time suggest there is no prothrombotic potential.
  - Idarucizumab completely reversed dabigatran induced effects on ETP.
  - Re-exposure after 2 months was well tolerated and the PD effects were the same as the initial dose.
  - There was no obvious effect of renal function on the reversal of the dabigatran anticoagulant effect of a 5 g dose.

- There were no obvious effect of race (Japanese patients), sex (19 female patients in the Phase I studies) and age.
- Where two 2.5 g doses were given the onset of action was within minutes of the first dose as measured by dTT, ECT, and aPTT.
- Anti-idarucizumab antibodies (ADA) had minimal impact on mean Cmax and AUC.

Efficacy

- Study 1321.3 (RE-VERSE AD) This was an interim analysis of the data from 123 patients from an ongoing Phase III, multinational, multicentre, open label, single arm study (case series) investigating the efficacy and safety of the reversal of the anticoagulant effects of dabigatran by the iv administration of 5 g idarucizumab. Idarucizumab was administered as two 2.5 g IV doses 15 minutes apart. Patients had 3 months of follow up post dose. Patients were ≥ 18 years, and taking dabigatran. Group A included dabigatran treated hospital emergency department patients with uncontrolled bleeding that required urgent medical or surgical treatment. Group B included dabigatran treated ED patients that required emergency surgery or other medical procedure necessitating rapid reversal of dabigatran. The main exclusion criteria for Group A were bleeding manageable with standard care, no clinical signs of bleeding, contraindication to the study medication (including hypersensitivity and hereditary fructose intolerance); and for Group B the main exclusion criteria were, in addition to the above contraindications, elective surgery or procedure or procedures/surgeries with a low risk of bleeding. The study is ongoing with a planned enrolment of 300 patients.
- There were 66 bleeding patients (Group A) and 57 patients needing surgery or a procedure (Group B), with a median age 77 years, mostly (85%) white, male (52.8%), with a median body weight of 72 kg and a median Cr Cl of 68.4 mL/min and mostly (95%) taking dabigatran for stroke prevention in atrial fibrillation. Most had a background of hypertension (77%), congestive heart failure (39%) diabetes (27%), coronary artery disease (31%), prior stroke (28%) and prior TIA (11%).
- About 61% and 60% were aged ≥ 75 years (about 18% and 21% ≥ 85 years) in Groups A and B, respectively. CrCL < 30 mL/min was more common in Group B (21%) than group A (11%), but Cr CL ≥30 - <50 mL/min was more common in Group A (30%) than Group B (18%). The majority of patients in each group (67% Group A and 63% Group B) were taking dabigatran 110 mg BD, with 29% in Group A and 32% in Group B taking dabigatran150 mg BD and only 1 patient (in Group A) taking 75 mg BD. Five patients were taking other dosage regimens. The median time from the last dose of dabigatran was 15.6 h (range 1.5 to about 94 h), with about 1/3 last dosed within 12 hours of idarucizumab treatment and 26% between 24 and 48 h. In Group A, 42% had last dosed between ≥ 12 and < 24 h.
- The median baseline total dabigatran concentration was 114 ng/mL (range 5.5 to 3600 ng/mL). The two patients with the highest dabigatran concentrations were not bleeding (Group B). Twenty two patients had normal dTT at baseline and 9 patients had normal ECT.
- Of the 66 patients in Group A, 41% had GI bleeding, 36% had intracranial bleeding and 18% had trauma related bleeding. Severe or life threatening GUSTO bleeding was reported in 71%. Diluted thrombin time was elevated in 78% and 72%, and thrombin time was elevated in 96% and 95% of patients in Groups A and B, respectively.
- Of the 57 patients in Group B, 23% has fractures, 12% had gall bladder disease requiring cholecystectomy, 9% had acute renal insufficient requiring catheter placement for dialysis, 7% had joint or wound infection, 5% had acute appendicitis, small bowel obstruction or bowel perforation. Three patients did not undergo the

planned surgery or procedure (1 had taken an overdose of 125 dabigatran capsules and idarucizumab was given in preparation for insertion of a catheter for dialysis that was not required after clotting tests were normalised with the use of idarucizumab, and 2 patients were too unstable for surgery due to their underlying pathology).

- The median total dabigatran concentration was 132 ng/mL (range 5.5, 886.0) in Group A and 114 ng/mL (range 6.9, 3600) in Group B.
- This was an interim analysis and about 50.4% had reached the three month follow up, 23.6 % of patient did not complete the 3 months observation time (19.5% because of AE) and the remainder had observation ongoing at the time of reporting. There was 1 major protocol variation in a patient with a metastatic melanoma misdiagnosed as an intracranial haemorrhage. This patient died 105 days later from malignancy progression.
- The efficacy assessment was based on clotting tests after the administration of idarucizumab. Serial plasma samples for clotting tests were measured at baseline, between the administration of the 2.5 g idarucizumab vials, and thereafter at 10-30 minutes, 1, 2, 4, 12 and 24 h. For this endpoint each patient acted as his/her own control so reversibility could be calculated using the following formula:

$$\text{Reversal} = \frac{\text{predose coagulation test} - \text{minimum postdose coagulation test}}{\text{predose coagulation test} - 110\%\ \text{ULN}} \times 100$$

- The primary efficacy endpoint was the central laboratory determination of the maximum reversal of the anticoagulant effect of dabigatran in the first 4 h after infusion as measured by ECT or dTT. Ninety of the 123 patients had central laboratory data for dTT and ECT.
  - Reversal occurred immediately after the administration of the first vial of idarucizumab.
  - 100% reversal of dTT was achieved in 96.8% and 90.9% of patients in Groups A and B, respectively, and ≥ 80% reversal in 100% patients in both groups.
  - 100% reversal of ECT occurred in 100% and 91.2%, and ≥ 80% reversal in 100% and 97.1% of patients in Groups A and B, respectively.
- At 12 and 24 hours dTT was below the ULN in 90.2% and 80.7% of patients, in Groups A and B respectively. At 12 and 24 h ECT, they were below the ULN in 71.6% and 54.3%, in Groups A and B, respectively.
- A sensitivity analysis using the reversal calculation with 100% ULN showed 100% reversal of dTT was achieved in 97.5% evaluable patients in Group A and 92.9% of evaluable patients in Group B. Using ECT 100% reversal was achieved in 89.4% and 88.2% in Groups A and B, respectively. The differences between the test results may reflect different assay sensitivities.
- Reversal based on aPTT measured in the central laboratory or locally at the hospital site.
  - Local laboratory measurement of aPTT within 30 minutes post dose: reversal in 75.0% of Group A and 75.6% of Group B
  - Central laboratory aPTT, measured at 4 h post dose: reversal in 94.9% of Group A and 84.6% of Group B.
- Clinical outcomes of hospitalisation, bleeding status, use of blood products, and re-starting anticoagulant therapy were the secondary endpoints.
  - Hospitalisation:

  - Median hospitalisation was 8 days in group A (range 2-72) and 10 days in Group B (range 2-93).
  - Median ICU stay in both groups was 0 days, the mean stay was 2.5 days in Group A and 1.7 days in Group B.
- Bleeding status:
  - Group A bleeding cessation was determined by the investigator or treating physician for 48 patients (remaining 18 the bleeding site was unable to visualised or identified). For 44 of the 48 patients bleeding stopped in 72 h with a median of 9.8 h (range 0.2 h - 67 days).
  - Group B haemostasis was judged by the surgeon; 48/52 (92.3%) patients had normal haemostasis, 3 (5.8%) had mildly abnormal haemostasis (for example, slight oozing) and one patient was judged to have moderately abnormal haemostasis resulting in bleeding reported within 24 hours post-surgery.
- Use of blood products:
  - 34.8% of Group A and 15.8% of Group B had received bleed products (including volume expanders) prior to idarucizumab use.
  - After the first vial of idarucizumab about 61% of Group A and 35% of Group B were given blood products. Packed RBCs were given to 51.5% of Group A patients and 17.5% of Group B patients. Fresh Frozen Plasma was given to about 21% of Group A and about 16% of Group B.

There was no control group so it is difficult to draw firm conclusions based on the clinical outcomes.

- Recommencement of anticoagulant/antithrombotic/antiplatelet therapy:
  - 71.2% of Group A and 86% of Group B recommenced a therapy of this type. 25.8% and 59.6% of Groups A and B respectively recommenced dabigatran, and 12.1% of Group A and 43.9% of Group B had bridging therapy prior to this recommencement.
  - Median time to recommencement of therapy was 4.57 days in Group A (range 0.16 to 77.23) and 1.31 days in Group B (range 0-40.77 days). The median times to recommencement of dabigatran was 17.46 days (0.34 to 90.63) and 6.49 days (1.05 to 63.31) for Groups A and B, respectively.
- Repeated dosing:
  - 2 patients given an additional 5 g, one at about 14 h after the first dose based on rising dabigatran levels and coagulation measurements, and the other about 62 hours due to re-elevation of aPTT and re-bleeding.

Safety

- A total of 406 adults (283 in Phase I studies and 123 in the Phase III study) were exposed to at least 1 dose of study drug in the clinical trial programme, of those 347 were exposed to at least one dose of idarucizumab, and 240 were exposed to a combination of dabigatran and idarucizumab.
- In the Phase I studies 15.6% of patients received 5 g of idarucizumab, and 12.1% received > 5 to 8 g of idarucizumab, and of the patients taking idarucizumab and dabigatran together about 30% received 5 g idarucizumab. Most (80-90%) received idarucizumab as a single infusion and only 7.7% and 4% received two 2.5 g doses separated by 15 minutes. Most were White, male and aged 19 to 44 years. Across the Phase I studies AEs were reported by approximately 25% of patients that received either idarucizumab or placebo. AEs were reported in 27.1% with idarucizumab alone

and 34.3% of placebo alone. AEs were reported for about 34% of dabigatran subjects only compared with 27% of dabigatran plus idarucizumab subjects (most were in the DE pre-treatment phase of the study). The events were mostly mild. Overall, idarucizumab was well tolerated. The most frequent event was headache (7.8%) with pre-treatment with dabigatran and before the idarucizumab dose (5.4% in the idarucizumab group and 1.9% in the placebo group), and in 8.4% of the idarucizumab only patients. Skin irritation (2.7%) and dizziness (2.2%) were also more frequent with idarucizumab ± dabigatran compared with placebo ± dabigatran. Treatment related AEs in Phase I studies were more common in the DE only arms compared with idarucizumab and dabigatran (overall 6.7% versus 3.1%). Epistaxis in DE group was reported in about 2% of patients and in 0.4% of the idarucizumab group. No deaths or SAEs occurred in the Phase I studies. There were no discontinuations because of AEs in any of the studies.

- In the Phase III study 103 AEs were reported for the 123 patients, for 89.4% of Group A and 77.2% of Group B. In the Phase III studies about 5% or more patients reported the AEs of headache, pneumonia (7/123, 5.7%), anaemia (7/123 5.7%), hypokalaemia (9/123, 7.3%), delirium (9/123, 7.3%), constipation 8/123 (6.5%), and pyrexia (7/123, 5.7%). The most common (≥ 5% patient) in Group A patients were delirium (10.6%), pyrexia (9.1%), constipation (9.1%), hypokalaemia (9.1%), urinary tract infection (7.6%), headache (7.6%), arthralgia (6.1%) and thrombocytopenia (6.1%) and in Group B were pneumonia (7%), diarrhoea (7%), anaemia (5.3%), and hypokalaemia (5.3%). The Treatment related AE epistaxis occurred in 2 patients, was short lived (1 and 2 minutes) and occurred some days after the idarucizumab (2 days and 7 days, respectively).
- Death was reported for 26/123 patients in the Phase III study, 13 in each treatment group: 11 within 1 day of idarucizumab from CV events (5), ICH progression (2), septic shock (2), peritonitis (1), and respiratory failure (1). Another 7 patients died on Days 1-30 after idarucizumab from CV events (4), ICH progression, cerebral infarction, multiple organ failure (MSOF). A further 8 patients died on 31-106 days after idarucizumab from malignant disease (3), pneumonia (2), GIH, Parkinson's, general health deterioration. None of the events were considered related to idarucizumab. SAEs were reported for in 47% of Group A and 38.6% of Group B with 53 events overall, including the 26 patients with events leading to death. The SAEs included 5 patients with thrombotic events; 3 in Group A (1 non ST elevation myocardial infarction [STEMI], one atrial thrombus with DVT and pulmonary embolism (PE), both in patients with intracranial haemorrhage in whom no antithrombotic treatment was started, and 1 DVT and PE two days after cessation of treatment for a GI bleed),and 2 in Group B (1 Right middle cerebral artery [MCA] stroke having stopped dabigatran for surgical management of an infected knee joint, with a post procedural rectal bleed on low molecular weight heparin (LMWH) that had also been ceased, and 1 bilateral below knee DVT in a patient admitted for surgery to treat cholecystitis). Two patients had elevated cardiac enzymes and ST segment abnormalities but had no diagnosis of MI.
- Three patients met the laboratory criteria for Hy's Law in the setting of cholelithiasis (1), renal and hepatic failure (1), and sepsis with MSOF (1).
- There was no signal for deterioration in renal function. There was a mean reduction in serum creatinine in both treatment groups in the Phase III study on a variable baseline. The highest baseline creatinine was 885 µmol/L.
- Immunogenicity:
  - Overall, across the Phase I studies 36/283 (13%) patients had pre-existing antibodies to idarucizumab, mostly to the C-terminus of idarucizumab and titres

were low. There was no effect of ADA on the reversal of dabigatran-induced anticoagulation as measured by dTT and ECT. In the Phase III study immunogenicity was available from 47 patients with a pre-and post-dose sample. Two patients had baseline non-specific ADA to the non-variable site of idarucizumab (C-terminus), persisting in both patients at 30 days. Treatment emergent antibodies were reported for 18 patients from the Phase I studies and one patient in the Phase III study. In these patients titres were low, and there was no apparent effect on dabigatran reversal. It is likely that, given the large dose of idarucizumab relative to the antibody titre any negative effect directly due to antibodies is likely to be overwhelmed by large dose of idarucizumab. Few patients had repeated doses of idarucizumab so it is difficult to draw conclusions about the impact of antibodies to idarucizumab in patients requiring additional treatments.

– In addition to the pyrexia events other possible hypersensitivity events included bronchospasm (n = 1) and hyperventilation (n = 1), rash (n = 2) and itchiness (1). There were no reported cases of anaphylactic shock or angio-oedema.

Risk management plan

The Pharmacovigilance and Special Access Branch has reviewed EU RMP version 2.0 and the ASA version 2.0 and has advised that the RMP documents require amendment as there are outstanding issues . These include:

- Inclusion of the educational materials as additional Risk Minimisation activities in the ASA
- Removal of the reference to the Special Access Scheme in the educational materials
- Addition of a precaution about transient proteinuria in the PI
- Inclusion of Australian patients in the global drug administration surveillance program for idarucizumab

Risk-benefit analysis

Delegate's considerations

Efficacy

- Idarucizumab is a specific binder of dabigatran with a much higher affinity for dabigatran than dabigatran has for thrombin. Idarucizumab has a 1:1 stoichiometric relationship with dabigatran, and a mass ratio of about 100:1. It needs to attain equimolarity or higher relative to plasma dabigatran to sustain the reversal of the effects of dabigatran. It has a rapid 'on rate' (within 5 minutes) and very slow 'off rate'. Idarucizumab has not been shown to bind or modulate clotting factors or co-factors in the coagulation cascade, so has no anticoagulant effect or prothrombotic effect.
- The efficacy of idarucizumab was demonstrated open label single arm study with data from an interim analysis of 123 patients enrolled as of the 1 April, 2015 cut-off date. Of those, 85% were White with small numbers of patients were of Asian ethnicity. The generalisability of the findings of this study for the Australian community is based on the assumption that the effects of dabigatran on the coagulation cascade and the binding of idarucizumab to dabigatran is independent of patient ethnicity. Idarucizumab patients were older than RE-LY study that supported the indication for the prevention of stroke and systemic embolism in patients with one or more risk factors for stroke (77 versus 71.5), were less likely to be male (52.8% versus 64%),

were lighter (median weight 72 kg versus 82 kg), and had worse renal function (median CrCL 68.4 mL/min versus 55.1 mL/min).

- The open label single arm study design is reasonable given that there is no established effective non-specific treatment regimen for dabigatran induced bleeding and there is no alternative method of rapid reversal (within minutes) of the anticoagulant effect of dabigatran in circumstances where urgent procedures including surgeries would provide optimal patient care. The sponsor relies on the reversal of dTT and ECT, sustained over 12 to 24 h, as a surrogate for clinical efficacy. Causes of bleeding can be complex and reversal of anticoagulation may not result in immediate cessation of bleeding, so this approach is reasonable. As there is no control group interpretation of the clinical outcomes is limited.
- Two doses 2.5 g given 15 minutes apart can reverse and sustain the reversal of the anticoagulant effect of DE for at least 24 hours in the majority of patients although in a few patients there was an increase in dTT beginning at 12 h and increasing to 24 h, attributed to dabigatran redistribution because the binding of the dabigatran complex is very tight. Within the limitations of the data there were no differences in response between males and females.
- Re-initiation of dabigatran 24 h after an idarucizumab dose resulted in unbound dabigatran concentrations and anticoagulant activity similar to the pre-idarucizumab findings in healthy volunteers. In patients in the Phase III study the recommencement of anticoagulants was more cautious, as anticipated by the clinical setting, and 8 of 17 patients in Group A and 25 of 34 patients in Group B had bridging therapy prior to dabigatran re-commencement. There is concern that early recommencement in patients with renal disease.
- Pre-exiting Ab with cross-reactivity found in 13% (non-specific to the C-terminus end, that is, not the end binding to DE), and had no impact of coagulation parameters dTT and ECT.

Safety

- Idarucizumab in its proposed will generally be used in a hospital setting, and under direct health professional supervision. Overall idarucizumab was well tolerated. Although there were 26 deaths in the Phase III study the two groups within the study population had an underlying high risk of death and the causes of death for each of the patients were not attributed to the use of idarucizumab. The thrombotic events following the use of idarucizumab reflect the underlying thrombotic risks in a high risk population and under high risk circumstances (for example, surgery, post transfusion, and in hospital). Across the clinical trial programme the events were acceptable in the clinical context in which idarucizumab is likely to be used. The small patient numbers in the Phase III study are insufficient to detect uncommon and rare events, and the absence of comparator group limits the interpretation of the events.
- Idarucizumab is a Fab fragment and has no Fc region so has low potential for reactions associated with Fc such as cytotoxic effect function through complement or interactions Fcγ receptors. Low numbers of patients had pre-existing antibodies to idarucizumab, mostly to the non binding end of the molecule and the titres were low. Small numbers of patients and healthy volunteers have been exposed to idarucizumab so the potential for hypersensitivity reactions with repeated exposure has not been well characterised. The sponsor has included hypersensitivity in the precautions section, but has not included this as a contraindication.
- The proposed Praxbind formulation contains up to 4 g of sorbitol, to support the osmolality of the drug product. This is of concern in patients with hereditary fructose intolerance. Sorbitol is a precursor of fructose, and the parenteral administration of

sorbitol to affected individuals has been associated with profound metabolic abnormalities and deaths. The sponsor has included hypersensitivity in the precautions section, but has not included this as a contraindication.

Indication

- The proposed indication is:

  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.*

  Continued approval for this indication may be contingent upon the results of an ongoing cohort case series study.

  The clinical evaluator considered it important to convey to prescribers that the evidence to support the indication is limited. The wording is based on the US label which describes the approval of Praxbind as having been under 'accelerated approval'. Australia does not have a provisional registration approval pathway, but this may be (incorrectly) implied by the qualifying sentence following the main part of the indication, and it is recommended that the sentence is deleted. The limitations of the data can be described in the Precautions section and the Indication should therefore read:

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

  - *for emergency surgery/urgent procedures*
  - *in life-threatening or uncontrolled bleeding.*

  It is recognised that there may be generic dabigatran etexilate products on the Australian market in the future, and that specific mention of one trade named product is unnecessarily restrictive, so it is proposed that 'Pradaxa' is removed from the indication.

  There is a potential application for idarucizumab in patients with overdose. Actively bleeding patients with an overdose are covered by the proposed indication, as is use prior to a procedure such as the insertion of a catheter for haemodialysis. The patient at risk of a bleeding event but not requiring an immediate procedure is not included in the indication, however this statement applies to all patients regardless of whether the dabigatran exposure resulted from compliance with recommended dose, medication errors or deliberate self-harm.

Dose

The 5g total dose is likely to reverse the dabigatran effect in the majority of clinical settings and is supported by evidence from the Phase III study.

Data deficiencies

- The single pivotal study is a small open label cohort study that is ongoing. No long term outcomes have been reported with use of idarucizumab. There is limited repeat dose exposure data. There are no paediatric data but this is noted in the PI.

Conditions of registration

The following are proposed as conditions of registration:

- There will be a condition of registration for the implementation of an EU RMP with an ASA.
- Provide the final clinical study report for Study 1321.3 to the TGA for evaluation, as soon as possible after completion, for evaluation.
- There will be batch release conditions imposed as a condition of registration.

Questions for the sponsor

1. Please explain the elimination pathway for the dabigatran-idarucizumab complex.
2. In the initial study report for Study 1321.3, 10 of 13 patients with PK measurements had detectable idarucizumab 24 h after dosing. Please comment on the likely implications for recommencement of dabigatran after 24 hours. Should dTT or another measure of the anticoagulant effect of dabigatran be performed to assess the presence of an effective dose of dabigatran?
3. Please explain the rationale for a single 5 g total dose for idarucizumab, given this may be in excess of requirements to bind the total body dabigatran load in many patients?
4. In Study 1321.3, hypokalaemia was reported as an AE in 9.1% of patients in Group A, but not present in any of these patients at baseline. Please comment.
5. There are clinical circumstances in which patients < 18 years of age may benefit from idarucizumab treatment, for example, pre-procedure or if there is accompanying major bleeding. How does the sponsor plan to investigate the use of idarucizumab in children?
6. Please describe the drug administration surveillance program that is proposed for the EU. What outcome data and other clinical information (for example, use of blood products, indications for use) are planned for collection? Will repeated dosing be captured in this program?
7. Please provide any updated safety information from Study 1321.3, including any post market data since launch of idarucizumab internationally.
8. Please address any outstanding issues with the RMP in the pre ACPM response.

Proposed action

The Delegate has no reason to say, at this time, that the application for idarucizumab should not be approved for registration.

Summary of issues

- Whether the limited safety and efficacy derived from one small, single arm, ongoing, open label Phase III study is sufficient for approval.
- Data on repeated dosing are limited. Most repeated dosing has occurred in 6 healthy volunteers with 2.5 g.
- Whether the whole 5 g is a necessary dose in all circumstances as this may have implications for the recommencement of dabigatran anticoagulation, for example, after the emergency surgery or procedure.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Please comment on the adequacy of the evidence from the ongoing, small, single arm, open label Phase III case series to support the efficacy and safety of idarucizumab for the proposed indication.
2. The sponsor does not propose to include hypersensitivity to idarucizumab or its excipients, or hereditary fructose intolerance as a contraindication to the use of idarucizumab. The sponsor has stated in the Section 31 responses that patients treated with idarucizumab are treated under emergency conditions which would allow treatment of events associated with hypersensitivity accordingly. Should 'hypersensitivity' or 'hereditary fructose intolerance' be contraindications or is the sponsor's justification acceptable? Should hypersensitivity to idarucizumab or hereditary fructose intolerance be contraindications to the use of dabigatran?
3. Please comment on the adequacy of the information about the use in patients with moderate to severe chronic kidney disease? Are extra precautionary statements in the PI warranted?
4. The patients in the clinical trials have been adults, and the proposed indication does not specifically exclude children. Does the committee have specific concerns about the potential for the use of idarucizumab in children?
5. Idarucizumab has a 1:1 stoichiometric relationship with dabigatran. Should dosing based on measured dabigatran concentration be considered in circumstances where dabigatran levels are available?
6. Please comment on the clarity and accuracy of the PI instructions for recommencement of anticoagulation including dabigatran after the administration of idarucizumab.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Presented here is Boehringer Ingelheim's (BI) pre ACPM response to the Delegate's Overview (DO) in relation to our application to register the new biological entity, Praxbind idarucizumab 50 mg/mL solution for injection/infusion vial.

- *Please comment on the adequacy of the evidence from the ongoing, small, single-arm, open label Phase III case series to support the efficacy and safety of idarucizumab for the proposed indication.*

Sponsor comment

BI is of the opinion that the data from Study 1321.3 (RE-VERSE AD) are adequate to support the safety and efficacy of idarucizumab in the target population. The data in patients in this modestly sized trial are consistent with the safety and efficacy demonstrated in double blind, placebo controlled Phase I studies in healthy subjects. The design of the Phase III study is limited by the low frequency of qualifying events, the urgency of intervention, the lack of standard treatment and the potential ethical dilemma of withholding a potential life-saving therapy from patients with life threatening conditions.

A large controlled trial with clinical outcomes as the primary endpoints would have been the best design for determination of efficacy and safety. However, such a trial would require thousands of patients, a large number of centres and countries and require many years to conduct, if it would be at all possible. The modest patient recruitment in our current open label, single cohort study in over 300 centres across 35 countries confirms the difficulty of conducting such a trial. After 1.5 years, less than 50% of sites in the current study have recruited a single patient. Thus, the design of our study was focused on

collecting safety data in patients and showing that idarucizumab reversed dabigatran in the target population.

RE-VERSE AD provides reliable evidence that idarucizumab immediately and completely reverses the anticoagulant effect of dabigatran in the target patient population. It has been consistently shown in patients with sepsis, trauma, intracranial haemorrhage, gastrointestinal bleeding and other conditions. These data are also consistent with the effects shown in controlled and blinded Phase I trials in volunteers. Thus, despite the life threatening conditions, multiple co-medications, variable presentations and multiple co-morbidities in this cohort, idarucizumab immediately reverses dabigatran. That is the primary endpoint in patients and the principle that was demonstrated in a rigorous manner in Phase I.

The clinical outcomes of the patients are more difficult to assess than pharmacologic reversal due to the variability of the patients at entry and the lack of a control group. Any possible clinical benefits like haemostasis and mortality are secondary endpoints and are subject to interpretation. For Group A, haemostasis is extremely difficult to show because of the inability to visualise most bleeds. In addition, the complicating conditions are multitude and different in every patient. In group B haemostasis is easier to judge because the surgeons know what level of bleeding to expect during the operation/procedure.

The assessment of safety in a single arm trial is also difficult, especially when the patients present with such a wide variety of conditions and co-morbidities. However, the trial supports the safety of idarucizumab based on an adverse event profile consistent with patients with life threatening conditions with multiple co-morbidities. Adverse reactions such as hypersensitivity and thrombosis might be expected, based on the fact that idarucizumab is a protein and affects the coagulation cascade (indirectly through its effect on the dabigatran-thrombin binding). However, the analysis of possible hypersensitivity in the RE-VERSE AD trial, summarised in the 4 Month Safety Update was shown to be low. Coupled with the low frequency (4%) and low titres of anti idarucizumab antibodies in Phase I subjects, the data support the safety profile. The summary of thrombosis data in the 4 Month Safety Update also confirms that any potential for a pro-thrombotic effect is low. Five of 123 patients experienced a thrombotic event, only one of which occurred within 72 h of idarucizumab treatment. None of the patients were on antithrombotic treatment at the time of the event. The events were consistent with the underlying risk of thrombosis in these patients.

In summary, the efficacy and safety profile of idarucizumab has been shown to be very consistent over the entire drug development program including preclinical, Phase I and Phase III trials.

- *The sponsor does not propose to include hypersensitivity to idarucizumab or its excipients, or hereditary fructose intolerance as a contraindication to the use of idarucizumab. The sponsor has stated in the Section 31 responses that patients treated with idarucizumab are treated under emergency conditions which would allow treatment of events associated with hypersensitivity accordingly. Should 'hypersensitivity' or 'hereditary fructose intolerance' be contraindications or is the sponsor's justification acceptable? Should hypersensitivity to idarucizumab or hereditary fructose intolerance be contraindications to the use of dabigatran?*

Sponsor comment

BI is of the opinion that the inclusion of hypersensitivity and patients with hereditary fructose intolerance (HFI) into the contraindication section of the PI may result in a treatment disadvantage for these patients.

Patients qualifying for idarucizumab administration for either uncontrolled or life-threatening bleeding or emergency surgery are usually under critically ill conditions.

Some of these patients are admitted to hospital unconscious. Under these emergency conditions the treating physician may not necessarily gain all relevant information concerning previous hypersensitivity reactions associated to Praxbind or information on HFI.

Idarucizumab will be administered in a hospital setting under emergency unit conditions. This allows immediate treatment of events associated with hypersensitivity or HFI.

On an individual case level the treating physician must weigh the risk (previous hypersensitivity reaction, HFI) against the benefit (normalisation of coagulation status to stop bleeding or to allow emergency surgery/procedure). Based on the individual situation, a patient may benefit from idarucizumab treatment although previous hypersensitivity reactions to Praxbind or HFI are known.

Therefore, treating physicians should have an idarucizumab treatment option whenever a positive benefit-risk assessment was made based on individual patient level. However, a contraindication for hypersensitivity or HFI may lead to the situation that a patient is not treated although the benefit-risk assessment is positive.

BI concludes that the inclusion of information on hypersensitivity and HFI in the Precautions section provides all relevant information and gives physicians the option to make an assessment for the best treatment option in an individual patient.

- *Please comment on the adequacy of the information about the use in patients with moderate to severe chronic kidney disease? Are extra precautionary statements in the PI warranted?*

Sponsor comment

BI considers it unnecessary to include an extra precautionary statement in the PI. The data support the recommendation that no dose adjustment of idarucizumab is required in patients with moderate to severe renal impairment and that there was no impact of renal impairment on the reversal effect of idarucizumab.

In the Phase I studies, volunteers with mild or moderate renal impairment have been recruited based on their CrCL values; these subjects can be regarded as suffering from chronic kidney disease. In contrast, for patients only a single measurement at baseline (at the time of inclusion into the trial) was taken. For these patients it is unknown whether the renal dysfunction according to CrCL categories was due to chronic kidney disease or due to acute renal failure as part of the emergency situation.

Pharmacokinetics

Volunteers with mild (CrCL ≥ 60 to < 90 mL/min) and moderate (CrCL ≥ 30 to < 60 mL/min) renal impairment were included in Study 1321.2. The popPK analysis identified renal function as a clinically meaningful independent covariate predicting idarucizumab PK. Impaired renal function resulted in decreased clearance, reduced initial half-life and increased AUC of idarucizumab. This information is reflected in the proposed PI.

Based on the available data from the dataset of 90 patients in Study 1321.3, idarucizumab AUC_{0-24} was calculated and separated by creatinine clearance (CrCL; [mL/min]) at baseline (0-<30; ≥30 to <60; ≥60 to <90 and ≥90). The results demonstrate that idarucizumab AUC_{0-24} correlates well with degrees of renal impairment (Table 7) and thus confirm the observations in Phase I.

Table 7. Idarucizumab AUC_{0-24} by CrCL category after administration of 5 g idarucizumab to patients in Study 1321.3.

Clearance categories [mL/min]	AUC_{0-24} [nmol*h/L]				
	N*	Median	Min	Max	gMean (gCV%)
0 - < 30	10	133000	87500	200000	129000 (26.1)
30 - < 60	31	74500	38600	153000	76900 (31.0)
60 - < 90	16	53000	40300	88500	54400 (21.6)
≥ 90	11	42900	24600	80400	43200 (33.4)

* Patients with missing serum creatinine at baseline are not included

Pharmacodynamics

Renal impairment does not affect the binding of idarucizumab to dabigatran and thus does not impact the reversal effect of idarucizumab. This information is reflected in the proposed PI. Renal impairment results in reduced clearance, that is, slower elimination of total idarucizumab (free idarucizumab plus idarucizumab bound to dabigatran). Especially in the early phase after idarucizumab dosing, there is a large surplus of free idarucizumab over dabigatran bound idarucizumab. Assuming that free and bound idarucizumab follow the same elimination route, this means that, especially in the early phase, predominantly free idarucizumab is eliminated. Renal impairment would thus delay the elimination of free idarucizumab and allow more time for dabigatran binding. This is considered to contribute to better effectiveness of the administered dose and does not warrant an additional precautionary statement. Since renal impairment also leads to increases in dabigatran concentrations, there is an increased amount of idarucizumab to potentially bind an increased amount of dabigatran.

Safety

Administration of idarucizumab to volunteers with mild or moderate renal impairment as well as patients with different stages of renal impairment was safe and well tolerated. In the RE-VERSE AD trial (study 1321.3), 40% of patients had moderate or severe renal impairment. No adverse reactions or lack of efficacy could be identified in these patients.

BI is of the opinion that an extra precautionary statement in the PI is not warranted.

- *The patients in the clinical trials have been adults, and the proposed indication does not specifically exclude children. Does the committee have specific concerns about the potential for the use of idarucizumab in children?*

Sponsor comment

Although the indication statement does not specifically exclude children, the current proposed PI does include the precautionary statement "The safety and efficacy of Praxbind in the paediatric population has not been established" under the section "Use in Specific Populations".

Dabigatran etexilate is not approved for use in children so use of idarucizumab in this patient group is expected to be low. In an attempt to gain some knowledge, BI has a trial planned in the paediatric population. Recruitment for the paediatric Praxbind trial is based upon recruitment of children into two paediatric trials of dabigatran etexilate. Given that the recruitment of paediatric patients into the dabigatran etexilate trials is expected to be slow and that the rate of bleeding or need for emergency surgery/procedures in children is expected to be extremely small, it may be very difficult to collect any data on Praxbind in this population.

Ultimately the decision on usage of Praxbind in children treated with dabigatran etexilate may be a consideration of the possible benefits in life threatening conditions weighed against the possible risks in the individual children.

- *Idarucizumab has a 1:1 stoichiometric relationship with dabigatran. Should dosing based on measured dabigatran concentration be considered in circumstances where dabigatran levels are available?*

Sponsor comment

The current proposed dosing regimen for idarucizumab administration to patients with emergency or life-threatening conditions is optimised for speed, simplicity and effectiveness.

A single infusion or bolus dose of 5 g is expected to reverse dabigatran in the vast majority of patients. To date, patient data have demonstrated the safety and effectiveness of this dose of idarucizumab in almost all patients. Results of clotting tests alone, without considering the clinical status of the patient, can be misleading. In addition, a general requirement for the use of clotting tests in context with idarucizumab treatment would introduce time delays, complexity and potential dosing errors in treating patients with these life threatening conditions.

Adjusting the dose of idarucizumab according to dabigatran concentrations or the pre-treatment level of anticoagulation has not been tested and may or may not be effective. The precise quantitative relationship between a test result and the amount of idarucizumab required does not exist. For example, a local aPTT of 55 seconds likely indicates that the patient is anticoagulated but does not predict whether, for example, 1, 2, or 5 g of idarucizumab will completely reverse the anticoagulant effect. In addition, locally available coagulation tests may have differing sensitivity and variability to dabigatran, making this even more complex.

Direct measurement of dabigatran concentrations is not widely available and certainly not available in a hospital within minutes in a life-threatening situation. If sampling and analysis was required before dosing, many patients who needed reversal would not be treated. Even if the concentration in plasma was available, an estimate of Vd is required to calculate body load. Vd is variable and may be even more variable in the target patient population. Calculations of dose based on this collection of information makes it more complex and the dosing may be subject to error.

The benefit of trying to individualise dose is to theoretically improve safety and efficacy in each individual patient. However, under the current dosing recommendation there is complete reversal in almost all patients, so it is unlikely that efficacy could be improved. The administration of the minimum effective dose theoretically maximises safety. However, no safety concerns have been identified to date, let alone any dose related adverse reactions. Therefore, there is no apparent safety benefit in tailoring a dose. As pointed out above, there are multiple issues in trying to establish an individual dose.

Therefore, BI concludes that there is no apparent improvement in the benefit/risk balance in tailoring the dose based on each individual while there is considerable risk and uncertainty in tailoring the dose in each patient.

- *Please comment on the clarity and accuracy of the PI instructions for recommencement of anticoagulation including dabigatran after the administration of idarucizumab.*

Currently the following wording is included in the 'Dosage and Administration, Restarting Antithrombotic Therapy' section in the proposed Australian PI:

> *Patients being treated with Pradaxa have underlying disease states that predispose them to thromboembolic events. Reversing Pradaxa 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. Idarucizumab is a specific reversal agent for dabigatran, with no impact on the effect of other anticoagulant or antithrombotic therapies. Pradaxa treatment can be initiated 24 h after administration of Praxbind (refer to dosing in PRECAUTIONS, Use in Specific Populations, Renal impairment).

From BI's perspective, the following key messages are presented in a short, simple and clear way:

- The physician is reminded that there is a consequence to not re-starting antithrombotic therapy.
- Dabigatran can be re-started 24 h after administration of Praxbind.
- Idarucizumab has no effect on other anticoagulants or anti thrombotics.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Praxbind solution for infusion containing 2.5 g in 50 mL of idarucizumab to have an overall positive benefit-risk profile for the delegate's amended indication:

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

- *for emergency surgery/urgent procedures*
- *in life-threatening or uncontrolled bleeding.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the CLINICAL TRIALS section of the PI and relevant section of the CMI referencing the limitations of the current data on safety.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Please comment on the adequacy of the evidence from the ongoing, small, single arm, open label Phase III case series to support the efficacy and safety of idarucizumab for the proposed indication.*

The ACPM advised that, despite the limitations of the data, idarucizumab can be indicated in emergency situations where there are no other evidence based options. The evidence provided is adequate to support this indication. More data will become available from on-going trials and post marketing reports; however, this is a potentially lifesaving treatment and no safety concerns were apparent. Nonetheless, the limitations of the data should be presented in the PI.

2. *The sponsor does not propose to include hypersensitivity to idarucizumab or its excipients, or hereditary fructose intolerance as a contraindication to the use of idarucizumab. The sponsor has stated in the Section 31 responses that patients treated with idarucizumab are treated under emergency conditions which*

would allow treatment of events associated with hypersensitivity accordingly. Should 'hypersensitivity' or 'hereditary fructose intolerance' be contraindications or is the sponsor's justification acceptable?

The ACPM advised that the sponsor's justification was acceptable.

Should hypersensitivity to idarucizumab or hereditary fructose intolerance be a contraindication to the use of dabigatran?

The ACPM was of the view that as idarucizumab is an emergency treatment hereditary fructose intolerance should not be a contraindication but affected patients should be informed before use and it should be included under PRECAUTIONS. The ACPM was of the view that this could also usefully be added to the dabigatran PI

3. *Please comment on the adequacy of the information about the use in patients with moderate to severe chronic kidney disease? Are extra precautionary statements in the PI warranted?*

The ACPM noted that idarucizumab is a short term treatment and the main issue seems to be the delay in clearance providing lengthened effectiveness, similar to the pattern seen with dabigatran in renal impairment. This may perhaps potentially increase the chance of a subsequent thrombosis but as yet no evidence has been found. The ACPM noted that kidney function is best quoted in terms of GFR or eGFR.

4. *The patients in the clinical trials have been adults, and the proposed indication does not specifically exclude children. Does the committee have specific concerns about the potential for the use of idarucizumab in children?*

The ACPM considered need for use would be rare in children and considered this would best be left as a clinician's decision. The committee noted the report of the planned extension study in conjunction with the current trial of dabigatran in children. The results of this study should be submitted to the TGA as soon as practicable.

5. *Idarucizumab has a 1:1 stoichiometric relationship with dabigatran. Should dosing based on measured dabigatran concentration be considered in circumstances where dabigatran levels are available?*

The ACPM agreed with the sponsor's response; measuring dabigatran levels to calculate dosage of the antidote would add complexity in a critical time-dependent clinical situation. A standard 5 g dose was used in the cohort study. Furthermore, it is unlikely that assays for dabigatran levels will be available in many hospitals.

6. *Please comment on the clarity and accuracy of the PI instructions for recommencement of anticoagulation including dabigatran after the administration of idarucizumab.*

The ACPM considered the statements in the PI were reasonable on the product's intended use; that reversal of the effects of dabigatran exposes patients to the thrombotic risk of their underlying disease and advise on resumption of anticoagulation as soon as medically appropriate. The PI also states that dabigatran can be recommenced 24 h after administration of idarucizumab and that dabigatran has no impact on the effect of other anticoagulants or antithrombotics.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Praxbind (idarucizumab [rch]) 50 mg/ml solution for injection/infusion vial indicated for:

> *Praxbind is a specific reversal agent for dabigatran and is indicated in patients treated with dabigatran etexilate (Pradaxa) when rapid reversal of the anticoagulant effects of dabigatran is required:*
>
> - *for emergency surgery/urgent procedures;*
> - *in life-threatening or uncontrolled bleeding*

Specific conditions of registration applying to these goods

- The idarucizumab EU-RMP, version 2.0, dated 19 November 2015, DLP 17 September 2015) with ASA (version 2.0, dated 11 April 2016), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following study reports:
  - The final clinical study report of Study 1321.3
  - The final study report of the idarucizumab drug administration surveillance program.
- All batches of Praxbind idarucizumab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- Each batch of Praxbind idarucizumab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

  The sponsor must supply:
  - Certificates of Analysis of the active ingredient (drug substance) and final product.
  - Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents of included).
  - Evidence of the maintenance of registered storage conditions during transport to Australia.
  - 3 to 5 vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI approved for Praxbind at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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