EU Risk Management Plan for Praxbind (idarucizumab)

Doc. No.: s00018805-07	
RMP version to be assessed as part of this application:	
RMP version number:	5.0
Data lock point for this RMP:	15 Oct 2019
Date of final sign off:	15 Aug 2024
Rationale for submitting an updated RMP:	To replace the brandname “Pradaxa” with “dabigatran etexilate” where appropriate
Summary of significant changes in this RMP:	None
Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	4.0
Approved with procedure:	EMEA/H/C/003986/R/0019
Date of approval (opinion date):	27 Jul 2020
QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder’s QPPV. The electronic signature is available on file.

PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Idarucizumab
Pharmacotherapeutic group (ATC code)	V03AB
Marketing Authorisation	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	Praxbind
Invented name in the EEA	Praxbind
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* Antidote
	Summary of mode of action Idarucizumab is a humanised antibody fragment (Fab) which binds to dabigatran with high affinity, ~300-fold more potent than the binding affinity of dabigatran for thrombin, thereby inhibiting the function of dabigatran.
	Important information about its composition Idarucizumab is a humanised Fab molecule derived from an IgG1 isotype molecule, directed against dabigatran, a direct thrombin inhibitor. The molecule is composed of the light chain (amino acids 1-219) and the heavy chain fragment (amino acids 1-225), covalently linked together by one disulphide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain. The theoretical average molecular weight of the Fab molecule is 47.8 kDa. Idarucizumab is expressed in 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.

Brief description of the product (cont'd)	
	Important information about its composition (cont'd) Idarucizumab (50 mg/mL) is formulated as a solution for i.v. injection or infusion. Idarucizumab (50 mg/mL) is sterile filtered and filled under aseptic conditions into 50 mL clear glass vials, which are closed by coated rubber stoppers and by an aluminium flip-off cap. It is tested for sterility as part of the release testing. Each unit of idarucizumab (50 mg/mL) has a nominal filling volume of 50.0 mL in a 50 mL vial. To ensure that 50.0 mL can be withdrawn from the vial, there is an overfill of 51.0 ± 0.5 mL. Idarucizumab (50 mg/mL) is formulated as a buffered, isotonic, preservative-free solution of 50 mg/mL active pharmaceutical ingredient (idarucizumab). The solution consists of active pharmaceutical ingredient, sodium acetate, sorbitol, polysorbate 20, and water for i.v. injection or infusion. Idarucizumab (50 mg/mL) is a colourless to slightly yellow, clear to slightly opalescent solution, with an osmolality of 270-330 mOsm/kg and a pH of 5.3-5.7. Idarucizumab should be stored in a refrigerator (2-8°C).
Hyperlink to the Product Information	Product information
Indications in the EEA	*Current* Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects of dabigatran is required: • For emergency surgery/urgent procedures • In life-threatening or uncontrolled bleeding
	Proposed Not applicable

Dosage in the EEA	*Current* Intravenous use. The recommended dose of idarucizumab is 5.0 g (2x 2.5 g).
	Proposed Not applicable
Pharmaceutical form and strength	*Current* 2.5 g/50 mL solution for injection/infusion
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
CHO	Chinese hamster ovary
EEA	European Economic Area
EU	European Union
Fab	Fragment antigen binding
i.v.	Intravenously
IgG	Immunoglobulin G
INN	International Non-proprietary Name
kDa	Kilodalton
RMP	Risk management plan

PART II SAFETY SPECIFICATION

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Hyperlink to the Product Information	Product information
Indications in the EEA	*Current* Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects of dabigatran is required: • For emergency surgery/urgent procedures • In life-threatening or uncontrolled bleeding
	Proposed Not applicable

Dosage in the EEA	*Current* Intravenous use. The recommended dose of idarucizumab is 5.0 g (2x 2.5 g).
	Proposed Not applicable
Pharmaceutical form and strength	*Current* 2.5 g/50 mL solution for injection/infusion
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
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EEA	European Economic Area
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Fab	Fragment antigen binding
i.v.	Intravenously
IgG	Immunoglobulin G
INN	International Non-proprietary Name
kDa	Kilodalton
RMP	Risk management plan

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1 INDICATIONS

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

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

Pradaxa (dabigatran etexilate) is currently approved in the EU for the prevention of VTEs in patients who have undergone major orthopaedic surgery, the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (SPAF), the treatment of acute DVT and/or PE and prevention of related death, and the prevention of recurrent DVT and/or PE and related death. Anticoagulation therapy can be associated with an increased risk of haemorrhage.

The following presents a summary of data of patients with haemorrhagic events and emergency surgery separated by the different Pradaxa (dabigatran etexilate) indications. Data on life-threatening and uncontrolled haemorrhagic events are only available from the RE-LY trial, but these events are regarded as a subset of MBEs, suggesting having lower rates than the MBEs presented below.

Haemorrhagic and emergency surgery/procedure events are acute conditions and therefore are better described by their incidence, see below.

SI.1.1 Pradaxa (dabigatran etexilate) indication: prevention of VTEs in patients who have undergone major orthopaedic surgery

Life-threatening or uncontrolled bleeding

No observational data on the incidence of haemorrhagic events in this Pradaxa indication is currently available. Below data from clinical trials are provided.

For this indication the active controlled trials 1160.19, 1160.24, 1160.25, 1160.48, 1160.64 and one placebo-controlled Phase II trial (1160.50) in Japanese patients were considered. Only results with patients treated with the suggested therapeutic dose (220 mg/day) and the results of the active comparator/placebo treated patients are presented in the following. In 2 of these trials (1160.24, 1160.50) the patients were randomised following surgery whereas in the remaining trials (1160.19, 1160.25, 1160.48, and 1160.64) the patients were randomised prior to surgery. These data are presented separately because the time point of randomisation may influence the incidence of haemorrhagic events.
In both post-operative randomisation trials, the number of patients with MBE was low (≤2.3%) and none of the events was fatal. Further details are given in the following 2 tables.

SI.Table 1 Summary of haemorrhagic events for trials 1160.24 and 1160.50 (Japanese patients) - post-operative randomisation

	Trial 1160.24	**Trial 1160.50**
	Dabigatran etexilate 220 mg	**Dabigatran etexilate 220 mg**
	N (%)	**N (%)**
Total treated patients	857 (100.0)	129 (100.0)
Patients with MBE	5 (0.6)	3 (2.3)
Number of MBEs	5	4
Fatal haemorrhagic event	0	0
Haemorrhage leading to re-operation	0	1
Symptomatic haemorrhage in critical organ	1	0
Requiring treatment cessation	0	4
Leading to >2 units transfusion in excess of what investigator expected	4	Not applicable
Leading to >4.5 units transfusion in excess of what investigator expected	n.a	1
Greater than 20 g/L fall in haemoglobin in excess of what investigator expected	4	0

The mean treatment duration was 10 days for patients with knee replacement surgery and 28-35 days for patients with hip replacement. Thus, no incidence rate is calculated.
MBE = major bleeding event defined by meeting at least one of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation

Data source: data on file, Pradaxa RMP v30.0, SVII.Table 2

SI.Table 2 Number (%) of patients with haemorrhages for study 1160.24 - post-operative randomisation

	Dabigatran etexilate 220 mg
Total treated patients, n (%)	857 (100.0)
Patients with MBE, n (%)	5 (0.6)
Patients with MBE or CRBE, n (%)	28 (3.3)
Patients with any haemorrhage, n (%)	74 (8.6)

The mean treatment duration was 10 days for patients with knee replacement surgery and 28-35 days for patients with hip replacement. Thus, no incidence rate is calculated.
MBE = major bleeding event defined by meeting at least one of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
CRBE = clinically relevant bleeding event defined as either: 1) spontaneous skin haematoma > 25 cm^2, 2) wound haematoma > 100 cm^2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 h if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator
Data source: data on file, Pradaxa RMP v30.0, SVII.Table 3

In the pooled pre-operative randomisation trials, the number of patients with MBEs was low. Further details are given in the following table.

SI.Table 3 Number (%) of patients with haemorrhages for trials 1160.19, 1160.25, 1160.48, and 1160.64 - pre-operative randomisation

	Dabigatran etexilate 220 mg
Total treated patients, n (%)	2835 (100.0)
Patients with MBE, n (%)	47 (1.7)
Patients with MBE or CRBE, n (%)	158 (5.6)
Patients with any haemorrhage, n (%)	349 (12.3)

The mean treatment duration was 10 days for patients with knee replacement surgery and 28-35 days for patients with hip replacement. Thus, no incidence rate is calculated.
MBE = major bleeding event defined by meeting at least one of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation
CRBE = clinically relevant bleeding event defined as either: 1) spontaneous skin haematoma > 25 cm^2, 2) wound haematoma > 100 cm^2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 h if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator
Data source: data on file, Pradaxa RMP v30.0, SVII.Table 5

Emergency surgery/procedures

No data on the incidence of emergency surgery/procedures are currently available for this Pradaxa indication.

SI.1.2 Pradaxa (dabigatran etexilate) indication: SPAF

Life-threatening or uncontrolled bleeding

Observational data from the EU

A Danish national cohort study using data from national registries from August 2011 to May 2013 including 7063 VKA-naïve dabigatran etexilate treated patients with atrial fibrillation (dabigatran etexilate 110 mg: n=3045; dabigatran etexilate 150 mg: n=4018) matched with 14 26 VKA-naïve warfarin treated patients and 4252 VKA-experienced dabigatran etexilate treated patients with atrial fibrillation (switchers from VKA) (dabigatran etexilate 110 mg: n=2038; dabigatran etexilate 150 mg: n=2214) matched with 8504 VKA-experienced warfarin treated patients analysed the incidence rates for any haemorrhage, major haemorrhage, fatal haemorrhage, gastrointestinal haemorrhage, and intracranial haemorrhage [P14-03813]. The mean ("intention to treat") follow-up time was 13.2 months. The following table summarises the incidence of haemorrhagic events in dabigatran etexilate users with atrial fibrillation.

SI.Table 4 Incidence (events per 100 PYs) in dabigatran etexilate treated patients stratified by dabigatran etexilate dose and VKA-naïve and VKA-experienced patients with atrial fibrillation

Outcome	Events/100 PYs	
	VKA-naïve patients	VKA-experienced patients
Any haemorrhage		
Dabigatran etexilate 110 mg bid	5.3	5.6
Dabigatran etexilate 150 mg bid	3.1	2.6
Major haemorrhage		
Dabigatran etexilate 110 mg bid	4.4	3.6
Dabigatran etexilate 150 mg bid	2.3	1.8
Fatal haemorrhage		
Dabigatran etexilate 110 mg bid	0.32	1.20
Dabigatran etexilate 150 mg bid	0.27	0.13
GI haemorrhage		
Dabigatran etexilate 110 mg bid	0.45	1.30
Dabigatran etexilate 150 mg bid	0.54	0.33
Intracranial haemorrhage		
Dabigatran etexilate 110 mg bid	0.51	0.78
Dabigatran etexilate 150 mg bid	0.27	0.54

Data source: [P14-03813] – Reported incidence rates are those from the "per protocol" (as-treated) analysis (censoring patients at the time of nonpersistence with treatment).

A higher crude incidence rate for bleedings for the 110 mg bid dose compared to the 150 mg bid dose was found but no increased risk when comparing dabigatran patients to VKA patients (e.g. major bleedings in VKA-naïve patients: dabigatran 110 mg bid vs VKA HR 0.91, 95% CI 0.73 - 1.14; dabigatran 150 mg bid vs VKA HR 0.67, 95% CI 0.53 - 0.85). Any differences in the crude incidence rates of bleedings might be driven by the differences in patient baseline characteristics (dabigatran 110 mg bid dose patients were on average older, had a higher HAS-BLED bleeding risk score and a higher proportion of patients with a history of bleeding compared to those patients on dabigatran 150mg bid).

Other analyses based on the same Danish registries, one considering 2012-2014 data [P16-06374] and another 2011-2015 data [P16-07890], have been published; however, they do not provide information about as-treated incidence rates.

Observational data from the US

Within the Mini-Sentinel project the event rate of GIH or ICH associated with use of dabigatran etexilate and warfarin in patients with atrial fibrillation between 19 Oct 2010 and 31 Dec 2011 was assessed [P17-02650]. In the cohort of patients with atrial fibrillation at risk for GIH or ICH, 20 870 new users of dabigatran etexilate without prior dabigatran etexilate use in the 12 months before (2 374 592 days at risk), and 35 458 new users of warfarin without prior warfarin use (3 807 255 days at risk) were analysed. Excluding individuals with prior dabigatran etexilate and warfarin use (mostly patients switching from warfarin to dabigatran etexilate), 9216 new users of dabigatran etexilate and 34 800 new users of warfarin were analysed (SI.Table 5) and a stratified analysis by age group performed (SI.Table 6).

SI.Table 5 Incidence in dabigatran etexilate treated patients with atrial fibrillation calculated by events/100k days at risk for GIH, ICH, and GIH or ICH

365 days "washout"	GIH events per 100k days at risk (number of events/people at risk)	ICH events per 100k days at risk (numbers of events/people at risk)	GIH or ICH events per 100k days at risk (numbers of events/ people at risk)
Dabigatran etexilate			
No previous dabigatran etexilate use	1.9 (45/20 929)	0.8 (19/20 927)	2.7 (63/20 870)
No previous use of warfarin or dabigatran etexilate	1.4 (13/9241)	0.9 (8/9234)	2.2 (20/9216)

The numbers of events are indicated in brackets (bold printed rows are the incident user excluding switchers).

Data source: [P17-02650]

SI.Table 6 Incidence in dabigatran etexilate treated patients with atrial fibrillation calculated by events/100k days at risk for GIH, ICH, and GIH or ICH stratified by age group

365 days "washout"	GIH events per 100k days at risk	ICH events per 100k days at risk	GIH or ICH events per 100k days at risk
Dabigatran etexilate			
No previous dabigatran etexilate use			
0 to 40 years (n=190)	0.0	0.0	0.0
41 to 54 years (n=1664)	0.6	0.6	1.2
55 to 64 years (n=4635)	0.7	0.4	1.1
65 to 74 years (n=6207)	1.4	0.7	1.9
75 to 84 years (n=6046)	3.4	1.1	4.5
85+ years (n=2128)	2.6	1.3	3.9
Dabigatran etexilate			
No previous use of warfarin or dabigatran etexilate			
0 to 40 years (n=125)	0.0	0.0	0.0
41 to 54 years (n=937)	0.0	0.0	0.0
55 to 64 years (n=2138)	0.0	0.5	0.5
65 to 74 years (n=2715)	1.8	0.4	1.8
75 to 84 years (n=2444)	2.8	1.6	4.4
85+ years (n=857)	1.2	2.5	3.7

Data source: [P17-02650] – Numbers in brackets are the numbers of users per age group for the GIH or ICH analysis.

Updated mini-sentinel analyses involving varying numbers of data partners were posted in 2016. One project titled "Anticoagulants and bleeding events" [P17-02648] used a time window from October 2010 to December 2012. Another project titled "New use of dabigatran or warfarin and gastrointestinal hemorrhage or intracerebral hemorrhage events" [P17-02649] used a time window from October 2010 to June 2013. No major differences were noted, although incidence rates tend to be lower in the later assessment: for patients with no warfarin or dabigatran use in the previous 365 days, incidence of GIH is 0.77/100k days at risk; incidence of ICH is 0.75/100k days at risk; incidence of GIH or ICH is 1.51/100k days at risk.

The US FDA reported an analysis of US Medicare data in May 2014 and published it in Circulation in October 2014 [P14-10426, P14-15648]. The observational study compares stroke, haemorrhage, MI, and mortality rates in new users (OAC-naïve patients) of dabigatran etexilate and warfarin in patients with atrial fibrillation using insurance-claim and administrative data for Medicare beneficiaries using propensity score matching for adjustment for potential confounding variables [P14-15648]. In this observational cohort study 134 414 Medicare patients who initiated dabigatran (n=67 207, contributing 18 205 PYs of on-therapy follow-up time) or warfarin for treatment of nonvalvular atrial

fibrillation between October 2010 and December 2012, all aged 65 years or older were evaluated, comprising 37 587 PYs of follow-up. In the following table, the incidence rates of the haemorrhage outcomes in dabigatran etexilate treated patients of the Medicare analysis are summarised.

SI.Table 7 Incidence rate and HR of haemorrhage outcomes in propensity score matched Medicare patients with atrial fibrillation

	Incidence rate per 1000 PYs
	Pradaxa (dabigatran etexilate)
Major haemorrhage	42.7
Gastrointestinal	34.2
Intracranial	3.3
Intracerebral	2.4
All hospitalised haemorrhages	59.3

Data source: [P14-15648]

A later Medicare study [P16-11555] included 118 891 patients who initiated treatment with dabigatran (n=52 240, contributing 15 524 person-years of on-treatment follow-up) or rivaroxaban from 04 Nov 2011 through 30 Jun 2014. Incidence rates reported for dabigatran were 23.3 per 1000 PYs for major gastrointestinal bleeding, 3.7 for intracranial haemorrhage, and 39.2 for all hospitalised extracranial bleedings.

A study conducted on the Department of Defense database [P15-10687] analysed 12 793 propensity-score matched patients per group who initiated dabigatran (mean duration of follow-up: 297.3 days) or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and July 2012. For dabigatran patients, reported incidence rates were 30.8 per 1000 PYs for major bleeding, 2.7 for major intracranial bleeding, 28.1 for major extracranial bleeding, and 25.4 for major gastrointestinal bleeding.

Another study conducted on two commercial health insurance databases (MarketScan, Truven and Clinformatics, Optum) [P15-10670] identified 19 189 dabigatran initiators (mean duration of follow-up: 5 months) from October 2010 through December 2012 propensity score-matched to warfarin. For dabigatran patients, reported incidence rates were 44.2 per 1000 PYs for major bleeding, 2.1 for major intracranial bleeding, 42.1 for major extracranial bleeding, and 26.5 for major gastrointestinal bleeding.

Clinical trial data

To supplement the observational data on MBEs with data on life-threatening haemorrhages, RE-LY clinical trial data are presented below.

For this indication only the active controlled trial 1160.26 (RE-LY with 18 113 patients) was included, due to the fact that in the remaining trials relatively small numbers of patients (<500 patients) were treated. RE-LY as a large trial allows for a better and more meaningful

interpretation of the data. As the treatment in this indication is considered a long-term treatment, the haemorrhagic event rates were calculated as yearly event rate. Fewer patients with MBEs were reported in the dabigatran etexilate treatment groups than in the warfarin treatment group, the rate of MBEs being dose-dependent: 2.92% per year for dabigatran etexilate 110 mg bid vs. 3.40% per PYs for dabigatran etexilate 150 mg bid. For life-threatening MBEs, the rates were 1.27% per PYs for dabigatran etexilate 110 mg bid and 1.52% per PYs for dabigatran etexilate 150 mg bid.

SI.Table 8 Frequency and annualised rate of haemorrhagic events for RE-LY (trial 1160.26)

	Dabigatran etexilate 110 mg bid	**Dabigatran etexilate 150 mg bid**
	N (%/a)	**N (%/a)**
Total treated patients	6015	6076
PYs	11 899	12 033
Patients with MBE	347 (2.92)	409 (3.40)
Life-threatening MBE	151 (1.27)	183 (1.52)
Other MBE	219 (1.84)	254 (2.11)
Patients with intracranial haemorrhage	27 (0.23)	39 (0.32)

%/a = yearly event rate
MBE = major bleeding event defined by meeting at least one of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation

Data source: data on file, main analyses for label updates, Table 4.2.1

Emergency surgery/procedures

No observational data on the incidence of emergency surgery/procedures are currently available for this Pradaxa indication. Emergency surgery data from the RE-LY trial are summarised in the table below.

The incidence rate of emergency surgeries/procedures requiring dabigatran etexilate treatment interruption in the RE-LY trial was 1.5% per 100 PYs for dabigatran etexilate 110 mg bid and 1.76% per 100 PYs for dabigatran etexilate 150 mg bid.

SI.Table 9 Incidence of emergency surgeries for trial 1160.26

	Dabigatran etexilate 110 mg bid (N=6015) N (%)	Dabigatran etexilate 150 mg bid (N=6076) N (%)
Total interruptions for surgery/procedure	2485 (100.0)	2635 (100.0)
Emergency procedure	182 (7.3)	214 (8.1)
Yearly event rate (100 PYs)	1.5	1.76

Date source: [U09-3249-02], Tables 15.1.4: 1, 15.3.1: 1, and 15.1.5: 8

SI.1.2.2 Pradaxa (dabigatran ezexilate) indication: treatment of acute DVT and/or PE and prevention of related death

Life-threatening or uncontrolled bleeding

No observational data on the incidence of haemorrhagic events in this Pradaxa indication is currently available.-Below data from clinical trials are provided.

For this indication, 2 active controlled clinical trials RE-COVER (1160.53) and RE-COVER II (1160.46) were analysed. In total, 5107 patients were treated with dabigatran etexilate 150 mg bid or warfarin for up to 6 months. The incidence rates (per 100 PYs) for haemorrhagic events in the dabigatran etexilate 150 mg bid treatment group were: MBE 1.0%, MBE/CRBE 4.4%, and any haemorrhagic event 14.4%. Further details are provided in the table below.

SI.Table 10 Number (%) of patients with haemorrhages for RE-COVER and RE-COVER II (trials 1160.53 and 1160.46) from start of double-dummy treatment (oral only treatment)

	Dabigatran etexilate 150 mg bid
Total treated patients, n (%)	2456 (100.0)
Time at risk (PYs)	1127.0
MBE rate/100 PYs	2.1
Patients with MBE, n (%)	24 (1.0)
Patients with life-threatening MBE, n (%)	4 (0.2)
Patients with MBE/CRBE, n (%)	109 (4.4)
Patients with any haemorrhagic event, n (%)	354 (14.4)

MBE = major bleeding event defined by meeting at least one of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation; CRBE = clinically relevant bleeding event defined as either: 1) spontaneous skin haematoma > 25 cm^2, 2) wound haematoma > 100 cm^2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 h if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator

Data source: data on file, Pradaxa RMP v30.0, SVII.Table 9 and Pradaxa SCS (DVT/PE treatment and prevention) [U07-3034], Table 2.1.3.2: 2

Emergency surgery/procedures

No data on the incidence of emergency surgery/procedures are currently available for this Pradaxa indication.

SI.1.2.3 Pradaxa (dabigatran etexilate) indication: Prevention of acute DVT and/or PE and related death

Life-threatening or uncontrolled bleeding

No observational data on the incidence of haemorrhagic events in this Pradaxa indication is currently available. Below data from clinical trials are provided.

For this indication one active controlled clinical trial (RE-MEDY, 1160.47) and one placebo controlled trial (RE-SONATE, 1160.63) were analysed. In total, 4199 patients were treated with either dabigatran etexilate 150 mg bid, warfarin, or placebo for up to 36 months in the warfarin controlled trial or up to 18 months in the placebo trial, respectively. The incidence rate for haemorrhagic events in the dabigatran etexilate 150 mg bid treatment group in the RE-MEDY (1160.47) trial were: MBE 0.9%, MBE/CRBE 5.6%, and any haemorrhagic event 19.4%. The incidence rates for haemorrhagic events in the dabigatran etexilate 150 mg bid treatment group in the RE-SONATE (1160.63) trial were: MBE 0.3%, MBE/CRBE 5.3%, and any haemorrhagic event 10.5%. Further details are provided in the table below.

SI.Table 11 Number (%) of patients with haemorrhages for RE-MEDY and RE-SONATE (trials 1160.47 and 1160.63)

	RE-MEDY (1160.47)	**RE-SONATE (1160.63)**
	Dabigatran etexilate 150 mg bid N (%)	**Dabigatran etexilate 150 mg bid N (%)**
Total treated patients	1430 (100.0)	684
Patients with MBE	13 (0.9)	2 (0.3)
Patients MBE/CRBE	80 (5.6)	36 (5.3)
Patients with any haemorrhagic event	278 (19.4)	72 (10.5)

MBE = major bleeding event defined by meeting at least one of the following: 1) fatal bleeding, 2) clinically overt bleeding in excess of what was expected and associated with >20g/L fall in haemoglobin in excess of what was expected, 3) clinically overt bleeding in excess of what was expected and leading to transfusion of >2 units of packed cells or whole blood in excess of what was expected, 4) symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding, 5) bleeding requiring treatment cessation bleeding leading to re-operation; CRBE = clinically relevant bleeding event defined as either: 1) spontaneous skin haematoma > 25 cm^2, 2) wound haematoma > 100 cm^2, 3) spontaneous epistaxis lasting >5 minutes, 4) spontaneous macroscopic haematuria or that lasting >24 h if associated with an intervention, 5) spontaneous rectal bleeding (more than a spot on toilet paper), 6) gingival bleeding lasting >5 min, 7) any other bleeding event judged as clinically relevant by the investigator

Data source: Pradaxa mastersheet 0266-13mas01, dated 18 Aug 2014, Tables 13 and 14

Emergency surgery/procedures

No data on the incidence of emergency surgery/procedures are currently available for this Pradaxa indication.

SI.1.3 Demographics of the population in the authorised indications and risk factors for the disease

SI.1.3.1 Demographics of the population in the authorised indications

In the following, demographic data on patients with haemorrhagic events are presented. Observational data is only available for the Pradaxa SPAF indication. Therefore, clinical trial data covering all Pradaxa indication is presented below as well. No data on the demographics of emergency surgery/procedure in dabigatran etexilate treated patients are currently available.

In an observational study using data from two US commercial health insurance databases (MarketScan and UnitedHealth) from October 2010 through December 2012, there were 19 189 dabigatran etexilate initiators (propensity score matched with warfarin treated patients) without anticoagulation in the past year, who had a diagnosis of atrial fibrillation not suggesting valvular disease [P15-10670]. During the average of 5 months follow-up period, 354 patients had a major haemorrhage. The demographics and patient characteristics at initiation of dabigatran etexilate of the 354 patients with major haemorrhage during follow-up is summarised in the table below.

SI.Table 12 Demographics and patient characteristics at initiation of dabigatran etexilate of the 354 patients with major haemorrhage during follow-up

Characteristic	**N (N=354)**	**%**
Age [years]	Mean: 73.6	SD: 11.1
Age categories		
18-54	20	5.65
55-64	73	20.62
65-74	77	21.75
75+	184	51.98
Sex		
Male	202	57.06
Female	152	42.94

Data source: [P15-10670]

An observational study included 191 dabigatran-treated patients with nonvalvular atrial fibrillation who presented with acute major bleeding to the ED at 5 sites in the US [P17-01857]. The table below presents patient characteristics at the time of presentation to the ED.

SI.Table 13 Demographics and patient characteristics at ED presentation of the 191 patients with major haemorrhage

Characteristic	N (N=191)	%
Age categories		
<65	21	11
≥65 to <75	45	24
≥75	125	65
Sex		
Male	98	51
Female	93	49
Major bleeding event anatomic location		
Gastrointestinal	118	62
Brain/Intracranial	36	19
Nontrauma	8	4
Trauma	28	15
Motor vehicle crash	1	1
Fall	27	14
Unknown location	1	1
Other locations	36	19

Data source: [P17-01857]

A study pooling data of 5 Phase III trials comparing patients treated with dabigatran etexilate or warfarin assessed the management and prognosis of major haemorrhages [P13-12677]. Characteristics of the patients with MBEs across the different clinical trials are shown in the table below.

SI.Table 14 Characteristics of the dabigatran etexilate treated patients with MBEs

	Dabigatran etexilate 110 mg	Dabigatran etexilate 150 mg
Patients randomised and treated, n	6015	10 740
Patients with MBE, n	262	365
Age, years, mean (SD)	75.9 (6.6)	75.1 (7.8)
Male sex, n (%)	170 (64.9)	234 (64.1)
Body weight, kg (SD)	81.4 (18.8)	82.1 (20.2)
Creatinine, µmol/L, median (range)	106 (44 - 968)	105 (43 - 800)
Creatinine clearance, median (range)	52 (5 - 155)	55 (5 - 199)

Data source: [P13-12677]

SI.1.3.2 Risk factors for haemorrhages

No observational data on the risk factors of haemorrhages in dabigatran etexilate-treated patients is currently available. Therefore, the risk factors for haemorrhages according to the Pradaxa SmPC are presented.

In general, the risk of haemorrhages increases with declining renal function. Renal function diminishes with age. The elimination of dabigatran may be reduced and exposure to dabigatran increased in elderly patients. Since these 2 variables are correlated, both increasing age and diminished renal function are associated with a higher risk of haemorrhage. The highest rates occur in the very elderly (age >75 years) with poor renal function. The table below summarises factors, which might increase the haemorrhagic risk for patients treated with Pradaxa.

SI.Table 15 Overview of factors which might increase the haemorrhagic risk

Pharmacodynamic and kinetic factors	Age ≥75 years
Factors increasing dabigatran plasma levels	*Major* • Moderate renal impairment (30-50 mL/min CrCl) • P-gp inhibitor co-medication *Minor* • Low body weight (<50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel
Diseases/procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative GI disease • Recent GI bleeding • Recent biopsy or major trauma • Recent ICH • Brain, spinal, or ophthalmic surgery • Bacterial endocarditis

Data source: Pradaxa SmPC section 4.4, Table 1 and Pradaxa RMP v30.0 [s00017740-26], Appendix 2, Table 1)

SI.1.4 The main existing treatment options

Some anticoagulants have a specific antidote that can be used in emergency situations where rapid reversal of anticoagulation is required, e.g. protamine sulphate for the heparins. Vitamin K and prothrombin complex concentrates can reverse the effects of warfarin and other vitamin K antagonists by replacing coagulation factors but in the case of vitamin K it takes a minimum of 6 hours until first signs of counteraction of the anticoagulant effect occur. It takes a minimum 24 hours until vitamin K completely counteracts VKA and re-dosing of vitamin K may also become necessary.

Before Praxbind became available, management of haemorrhages was limited to supportive care, administration of blood or blood products and, in suitable patients, consideration of haemodialysis to remove the drug [P12-13111, P13-12677]. There was no specific therapy for the management of dabigatran etexilate-associated haemorrhages or for patients treated with dabigatran etexilate requiring (emergency) surgery/intervention. In a recent publication, the periprocedural haemorrhage and thromboembolic events rates of patients treated with dabigatran etexilate and warfarin in the RE-LY trial were compared. Irrespective of knowing which patients had been on warfarin therapy (with the option to apply specific treatment, e.g. vitamine K application), no significant difference was observed in the rates of periprocedural major haemorrhage between patients receiving dabigatran etexilate 110 mg (3.8%), dabigatran etexilate 150 mg (5.1%), or warfarin (4.6%). Among patients having urgent surgery, similar rates of periprocedural major haemorrhage were observed between patients receiving dabigatran etexilate 110 mg (17.8%), dabigatran etexilate 150 mg (11.7%), or warfarin (21.6%). Patients receiving dabigatran etexilate were 4 times more likely to have their procedure or surgery within 48 hours of withholding anticoagulation, thus allowing an earlier intervention [P12-08518].

Due to the heterogeneity of the emergency surgery/procedure population, no main treatment options can be presented.

SI.1.5 Natural history of the indicated condition in the population, including mortality and morbidity

Observational data on mortality of patients with haemorrhagic events is currently scarce. In a study including 191 dabigatran-treated patients with nonvalvular atrial fibrillation who presented with acute major bleeding to the ED at 5 sites in the US [P17-01857], 12 subjects (6%) died before discharge. Clinical trial data for mortality of patients with haemorrhagic events covering all Pradaxa indication is presented below as well. Observational data on patients with haemorrhagic events are presented for the Pradaxa SPAF indication. No data on the mortality and morbidity of emergency surgery/procedure in dabigatran etexilate treated patients are currently available.

A study pooling data of 5 Phase III trials comparing patients treated with dabigatran etexilate or warfarin from assessed the management and prognosis of major haemorrhages [P13-12677]. The crude mortality in the 5 studies at 7 and 30 days after the onset of the first major haemorrhagic event among the dabigatran etexilate and the warfarin treated patients was 5.3% vs. 8.4% (p=0.045) and 9.1% vs. 13.0% (p=0.057), respectively. Adjusted for sex, age, weight, renal function at the time of the haemorrhage and additional antithrombotic therapy the OR for 30-day mortality in the combined dabigatran etexilate treatment groups was 0.66 (95% CI 0.44, 1.00; p=0.051). For the RE-LY population alone, the adjusted OR for 30-day mortality for the dabigatran etexilate treatment groups combined was 0.56 (95% CI 0.36, 0.86; p=0.009). In conclusion, the mortality after a major haemorrhage was not worse than after a warfarin-associated bleed.

Incidence of haemorrhagic events from a Danish national cohort study and incidence rates of haemorrhagic outcomes from an observational study (analysis of US Medicare data) are presented in Section SI.1.1.2 (SI.Table 4 and SI.Table 7).

SI.1.6 Important co-morbidities

In the following, comorbidity data on patients with haemorrhagic events or emergency surgery/procedures are presented.

The patients included in the Phase III trial 1321.3 had a high rate of comorbidities as reflected by both relevant medical history and baseline diseases [c12723965-01, Table 15.1.3: 2]. A review of relevant medical history indicated that the majority (78.3%) of the 503 patients had hypertension; 36.2% had congestive heart failure and 35.4% had coronary artery disease; and 30.2% had diabetes (Table 10.4.3: 1). Approximately 9% of patients had a prior TIA. Prior stroke was reported by 24.3% of Group A patients (dabigatran etexilate-treated patients with life-threatening or uncontrolled bleeding) and 17.8% of Group B patients (dabigatran etexilate-treated patients requiring emergency surgery or procedures for other morbidities).

SI.Table 16 Relevant medical history – Treated set

	Group A		Group B		Total	
	N	(%)	N	(%)	N	(%)
Total patients	301	(100.0)	202	(100.0)	503	(100.0)
Hypertension	237	(78.7)	157	(77.7)	394	(78.3)
Congestive heart failure	117	(38.9)	65	(32.2)	182	(36.2)
Atrial fibrillation	288	(95.7)	190	(94.1)	478	(95.0)
Diabetes	95	(31.6)	57	(28.2)	152	(30.2)
Coronary artery disease	110	(36.5)	68	(33.7)	178	(35.4)
Prior stroke	73	(24.3)	36	(17.8)	109	(21.7)
Prior TIA	27	(9.0)	20	(9.9)	47	(9.3)
Prior systemic embolism	20	(6.6)	16	(7.9)	36	(7.2)
Prior major bleeding	27	(9.0)	10	(5.0)	37	(7.4)
Active cancer	23	(7.6)	20	(9.9)	43	(8.5)

Data source: [c12723965-01], Tables 15.1.3: 2

Nearly all (95.4%) patients had other ongoing baseline conditions [c12723965-01, Table 15.1.3: 6]. As would be expected for a population with atrial fibrillation, more than half of the patients (60.0%) had underlying cardiac disorders. Nearly half of all patients had gastrointestinal or metabolic/nutrition disorders (49.5% and 50.1%, respectively), 26.0% had underlying infections and infestations, and 10.7% had hepatobiliary disorders. Renal and urinary disorders were cited for approximately 32.8% of the patients, including 10.1% with chronic kidney disease and 3.6% with renal failure. Renal function measured in patients in the emergency situation which led to enrolment into the trial may not necessarily reflect the renal function under stable conditions due to possible shock and other hemodynamic changes associated with the qualifying events. Other relevant baseline conditions (by preferred term) included osteoarthritis (14.7%), chronic obstructive pulmonary disease (13.7%), anaemia (11.1%), and hypothyroidism (8.7%).

In an observational study using data from two US commercial health insurance databases (MarketScan and UnitedHealth) from October 2010 through December 2012, there were 19 189 dabigatran etexilate initiators (propensity score matched with warfarin treated patients) without anticoagulation in the past year, who had a diagnosis of atrial fibrillation not suggesting valvular disease [P15-10670]. During the average of 5 months follow-up period, 354 patients had a major haemorrhage. The comorbidities and stroke/ haemorrhage risk scores at initiation of dabigatran etexilate (not at time of haemorrhagic event) of the 354 patients with major haemorrhage during follow-up can be found in the 2 tables below.

SI.Table 17 Medical history/comorbidities at initiation of dabigatran etexilate initiation of the 354 patients with major haemorrhage during follow-up

Medical history/comorbidities	**N (N=354)**	**%**
Coronary artery disease	153	43.22
Systemic embolism	7	1.98
DVT	9	2.54
PE	2	0.56
Hypertension	343	96.89
Diabetes	99	27.97
Hyperlipidaemia	179	50.56
Atherosclerosis	138	38.98
Heart failure (CHF)	86	24.29
Stroke	53	14.97
Intracranial bleeding	1	0.28
Haemorrhagic stroke	0	0.0
Ischaemic stroke	44	12.43
Previous TIA	21	5.93
Recent MI	19	5.37
Old MI	29	8.19
Peptic ulcer disease	39	11.02
Upper GI bleed	1	0.28
Lower/unspecified GI bleed	14	3.95
Urogenital bleed	0	0.0
Other bleedings	17	4.8

SI.Table 17 (cont'd) Medical history/comorbidities at initiation of dabigatran etexilate initiation of the 354 patients with major haemorrhage during follow-up

Medical history/comorbidities	**N (N=354)**	**%**
Peripheral vascular disease, PVD surgery	29	8.19
Prior liver disease	13	3.67
Cancer	48	13.56
Renal dysfunction	71	20.06
Acute renal disease	32	9.04
Chronic renal insufficiency	40	11.3

Data source: [P15-10670]

SI.Table 18 Stroke and haemorrhage risk scores at initiation of dabigatran etexilate of the 354 patients with major haemorrhage during follow-up

Risk score	**N (N=354)**	**%**
$CHADS_2$ score	Mean: 2.41	SD: 1.16
$CHADS_2$ score = 0-1	82	23.16
$CHADS_2$ score = 2	127	35.88
$CHADS_2$ score = 3+	145	40.96
CHA_2DS_2-VASc score	Mean: 3.84	SD: 1.65
CHA_2DS_2-VASc score = 0	0	0.00
CHA_2DS_2-VASc score = 1-2	32	9.04
CHA_2DS_2-VASc score = 3+	322	90.96
HAS-BLED	Mean: 2.71	SD: 1.16
HAS-BLED score = 0-1	52	14.69
HAS-BLED score = 2	110	31.07
HAS-BLED score = 3+	192	54.24

Data source: [P15-10670]

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ABBREVIATIONS

100k	100 000
ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
bid	*Bis in die*, twice daily
$CHADS_2$	Stroke risk score (congestive heart failure, hypertension, age >75, diabetes, prior stroke/transient ischaemic attack)
$CHADS_2$-VASc	Stroke risk score (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75, diabetes, stroke [doubled]-vascular disease, age 65-74, sex category)
CHF	Congestive heart failure
CI	Confidence interval
CRBE	Clinically relevant bleeding event
CrCl	Creatinine clearance
DLP	Data lock point
DVT	Deep vein thrombosis
ED	Emergency department
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GIH	Gastrointestinal haemorrhage
HAS-BLED	Haemorrhage risk score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly)
HR	Hazard ratio
ICH	Intracerebral haemorrhage
MAH	Marketing 20uthorization holder

MBE	Major bleeding event
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
OAC	Oral anticoagulant
OR	Odds ratio
PE	Pulmonary embolism
P-gp	P-glycoprotein
PVD	Peripheral vascular disease
PY	Person-year
RMP	Risk management plan
SCS	Summary of clinical safety
SD	Standard deviation
SmPC	Summary of product characteristics
SPAF	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
TIA	Transient ischaemic attack
US	United States
VKA	Vitamin K antagonist
VTE	Venous thrombotic event

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

SII.1.1 Toxicity

SII.1.1.1 Neutralisation of dabigatran's anticoagulant effects and durability

Idarucizumab is a humanised antibody fragment that binds dabigatran and its glucuronide metabolites with an affinity ~300-fold greater than the binding affinity of dabigatran to thrombin, resulting in rapid and durable neutralisation of dabigatran-associated anticoagulant effects [n00232054-01, n00231289-02, P13-05131, n00226711-03, and n00227451-03].

Due to the high affinity binding of idarucizumab to dabigatran, neutralisation of dabigatran's anticoagulant effect should be sustained in patients, regardless of any delay in elimination, e.g. renal impairment.

SII.1.1.2 Thrombosis

Although the idarucizumab binding site has similarity to portions of the thrombin binding site for dabigatran, idarucizumab did not bind to thrombin substrates and had no thrombin-like enzymatic activity [P13-05131, n00233139-01]. In addition, idarucizumab displayed no pro-thrombotic effects following administration to monkeys [n00230533-02].

Since idarucizumab binds dabigatran and dabigatran binds to thrombin, there is a theoretical possibility that anti-idarucizumab antibodies could bind to thrombin. However, this risk was not apparent in non-clinical toxicity studies, as neither idarucizumab nor the presence of anti-idarucizumab antibodies had any effect on coagulation indices in rats or monkeys [U12-3327-01, U12-3328-01, U13-3538-01, and n00230533-02].

No pro-thrombotic effects are anticipated in humans due to idarucizumab or due to potential formation of anti-idarucizumab antibodies. No effects on coagulation are anticipated due to idarucizumab or due to potential anti-idarucizumab antibodies.

SII.1.1.3 Bleeding

Reversal of dabigatran anticoagulant activity resulted in the restoration of normal fibrin deposition [n00237740-01] and in non-clinical bleeding models resulted in rapid cessation of dabigatran-associated bleeding [n00234943-01, n00237737-01, and n00231240-02].

Following neutralisation of dabigatran activity, a re-equilibration of sum dabigatran occurs between the plasma and extravascular compartments resulting in 5- to 10-fold elevations in LC-MS/MS detectable plasma levels of sum dabigatran in rats, monkeys, and swine [n00227451-03, n00231240-02, and U13-3539-01]. In animals, in the event idarucizumab levels were less than equimolar to re-equilibrated sum dabigatran, bleeding occurred from a

new wound site made after the re-appearance of low dabigatran levels, but bleeding did not reoccur at a wound site where haemostasis had already been established [n00238140-01].

These results illustrate the necessity to administer a sufficient dose of idarucizumab to humans to assure durable neutralisation of dabigatran anticoagulation in situations such as emergency surgery. They also demonstrate that low levels of dabigatran are not likely to cause a renewal of excessive bleeding at a wound site once haemostasis has occurred.

SII.1.1.4 Co-medications and procedures

In emergency situations of excessive bleeding, various measures are employed to promote coagulation and restore fluid volume. The ability of idarucizumab to neutralise dabigatran anticoagulation was not affected by agents used to replenish or supplement coagulation in emergency settings, such as PCC, activated PCC, or recombinant Factor VIIa [n00238187-01] and showed no binding difference in the presence of 50% haemodilution with volume replacement agents [n00230830-01].

Idarucizumab did not affect anti-platelet-induced bleeding of standard co-medications of patients on anticoagulant therapy [n00237733-01] and did not affect anticoagulation related to other oral or parenteral anticoagulants [n00238041-01].

The use of fluid restoration or agents to stimulate coagulation will have no effect on idarucizumab efficacy. Idarucizumab is specific for rapid reversal of dabigatran-associated anticoagulation and will not affect anticoagulation related to other oral or parenteral anticoagulants.

SII.1.1.5 Renal impairment

Idarucizumab, alone or bound to dabigatran, is controlled by the elimination pathway of idarucizumab, which is primarily by passive glomerular filtration and receptor-mediated renal reuptake/catabolism. This statement is supported by results in animal studies including idarucizumab and DE/idarucizumab plasma concentration-time profiles, PK parameters, idarucizumab and sum dabigatran urinary excretion, and immunohistochemical evidence of idarucizumab inside proximal tubule cells [U12-3083-01, U12-3326-01, U13-3539-01, and n00230533-02].

Non-clinical studies in 5/6 nephrectomised rats [U13-3340-01] demonstrated the substantial contribution of the kidneys in the elimination of idarucizumab and also illustrated the decreased renal clearance of idarucizumab anticipated in patients with renal impairment.

In view of the elimination route for both dabigatran and idarucizumab, special attention was given to renal effects in non-clinical toxicity studies. No renal toxicity was exhibited by monkeys exposed to idarucizumab alone or when administered after dabigatran etexilate daily for 2 weeks [n00230533-02]. Renal findings noted in 1 monkey receiving 12/500 mg/kg DE/idarucizumab twice [U12-3328-01] could not be aligned with the dosing regimen and the appearance and progression of toxicity, and in view of the lack of toxicity observed in the 2-

week monkey study, they were concluded to be related to the pre-existing poor health of this animal rather than toxicity of idarucizumab.

Due to the high affinity binding of idarucizumab to dabigatran, neutralisation of dabigatran's anticoagulant effect should be durable in renally impaired patients, regardless of the delay in elimination.

Since toxicity studies demonstrated a lack of treatment-related adverse renal effects in rats and monkeys, the potential for idarucizumab-related adverse renal effects in humans is considered low.

SII.1.2 Safety pharmacology

Core battery safety pharmacology studies (cardiovascular, respiratory, CNS) revealed no toxicity associated with administration of a single large dose level of 500 mg/kg idarucizumab to rats or monkeys or 12/500 mg/kg DE/idarucizumab to monkeys [U12-3327-01, U12-3328-01, and U12-3330-01].

The lack of toxicity in rats and monkeys supports a low incidence of adverse effects in humans.

SII.1.3 Other toxicity-related information or data

A series of safety pharmacology and general toxicology studies have been conducted, along with local tolerance and tissue cross-reactivity evaluations that support intravenous administration of idarucizumab to humans. No idarucizumab binding to human tissues was observed in a tissue cross-reactivity study [U12-3331-01].

The NOAEL of idarucizumab in the 4-week rat and 2-week monkey studies was the high-dose of 500 mg/kg/day [U12-3327-01, n00230533-02]. In monkeys, the high-dose of 12/500 mg/kg/day DE/idarucizumab was a NOAEL. No treatment-related changes in body weight, clinical observations, clinical pathology (haematology, plasma chemistry, urinalysis), ophthalmology, weights of major organs, or microscopic examination of organs were observed in either species. Idarucizumab plasma levels and exposure were adequate to determine its toxicity, as maximum plasma and exposure levels of 7-fold and 3- to 5-fold those in subjects aged 45 to 64 years (clinical trial 1321.2), respectively, were reached. Dabigatran/sum dabigatran levels in monkeys reflected those in humans administered the maximum recommended dose of 300 mg/day DE (150 mg bid).

Idarucizumab toxicokinetics and its efficacy were not impacted by the presence of anti-idarucizumab antibodies during treatment phase in studies of 2 weeks or longer. In toxicity studies in rats and monkeys, no adverse effect attributable to anti-idarucizumab antibodies were revealed. No evidence of glomerular damage suggestive of immune complex deposition was observed in the kidneys of rats or monkeys, and no granular deposits suggestive of immune complex deposition were seen following immunohistochemistry of the kidney in the 2-week monkey study. No treatment-related elevations in circulating immune complexes were noted in the 2-week monkey study. The only discernable impact of anti-idarucizumab

antibody presence was a hypersensitivity reaction during the third idarucizumab infusion in one 1 of 8 monkeys administered idarucizumab intermittently in a PK/PD study [U12-3849-01, U13-3539-01]. No other infusion reaction or other immunogenicity-related adverse reactions were observed in monkeys administered intermittent doses or rats and monkeys given daily repeated doses of idarucizumab, with or without DE, even though anti-idarucizumab antibodies were present.

There was no consistent evidence for the formation of anti-dabigatran antibodies in the 2-week monkey study [n00230533-02]. While in theory dabigatran could act as a hapten by binding to idarucizumab and inducing antibodies, indications that this occurred could not be found following assays for functional or total anti-dabigatran antibodies, re-administration of the potential hapten and measurement of complement, measurement of circulating immune complexes, or investigation of immune complex deposition by immunohistochemistry. Consequently, there is a low likelihood of anti-dabigatran antibody formation in humans.

The idarucizumab proposed commercial formulation was tolerated locally when given by intravenous and perivascular injection to rats, rabbits, and monkeys [U12-3327-01, U12-3328-01, U13-3538-01, and n00230533-02] and caused no haemolysis of human blood in vitro [U12-3289-01].

Idarucizumab is an antibody fragment that is produced by CHO cells and is characterised as a biotechnology-derived pharmaceutical, which in accordance with ICH S6(R1) does not require genotoxicity evaluation. In accordance with ICH M3(R2) and S1A and the proposed use of idarucizumab, administered intravenously at 5000 mg on 1 day in emergency situations, no chronic or carcinogenicity studies have been conducted. Women of childbearing potential are instructed to avoid pregnancy during treatment with dabigatran etexilate and it is recommended that the risks and benefits of dabigatran etexilate be weighed prior to use in pregnancy as animal studies have shown adverse effects on the foetus (addressed in the Pradaxa European Union summary of product characteristics); consequently, no reproductive toxicity studies have been conducted with idarucizumab.

The lack of toxicity in rats and monkeys supports a low incidence of adverse effects in humans.

Formation of anti-idarucizumab antibodies in rats and monkeys does not predict formation in humans, as idarucizumab is humanised. Consequently, a hypersensitivity reaction in monkeys is not predictive of an analogous response in humans and based on the totality of available information, the immunogenic potential of idarucizumab in humans is considered low.

Based on non-clinical data, the likelihood for formation of anti-dabigatran antibodies is low.

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ABBREVIATIONS

bid	*Bis in die*, twice daily
CHO	Chinese hamster ovary
CNS	Central nervous system
DE	Dabigatran etexilate
ICH	International Conference on Harmonization
NOAEL	No observed adverse effect level
PCC	Prothrombin complex concentrates
PD	Pharmacodynamic
PK	Pharmacokinetic
RMP	Risk management plan

MODULE SIII CLINICAL TRIAL EXPOSURE

Combined Phase I exposure is presented by the following treatment groups: dabigatran etexilate (pre-treatment), placebo, dabigatran etexilate+placebo, idarucizumab, dabigatran etexilate+idarucizumab, placebo/dabigatran etexilate+placebo, and idarucizumab/dabigatran etexilate+idarucizumab (designated in the following as “DE”, “placebo”, “DE+placebo”, “Ida”, “DE+Ida”, “placebo/DE+placebo”, and “Ida/DE+Ida” in the flow text and in-text tables.

Phase III exposure (i.e. patients being treated with dabigatran etexilate, trial 1321.3) is presented by the following 2 treatment groups, designated in the following as “group A” and “group B” in the flow text and in-text tables:

- Group A: dabigatran etexilate-treated patients with life-threatening or uncontrolled bleeding
- Group B: dabigatran etexilate-treated patients requiring emergency surgery or procedures for other morbidities

Groups A and B are not randomised groups.

SIII.1 CLINICAL TRIAL EXPOSURE IN PHASE I TRIALS IN SUBJECTS

Overall, 295 treated subjects were included in the Phase I clinical development programme. Out of these 295 treated subjects, 236 subjects received idarucizumab and 105 subjects placebo, regardless of DE pre-treatment. Overall, 153 of the 295 treated subjects received pre-treatment with DE. A comparable number of subjects received only idarucizumab (107 subjects) or DE+Ida (129 subjects). Further detail, also by trial, is given in the following table.

SIII.Table 1 Phase I treatment exposure - TS

		Placebo		Idarucizumab		Total		
	DE[1]	Placebo	DE+placebo	Ida	DE+Ida	Placebo/ DE+placebo	Ida/ DE+Ida	Overall
Number of subjects	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N**
Total Phase I								
	153 (100.0)	35 (100.0)	70 (100.0)	107 (100.0)	129 (100.0)	105 (100.0)	236 (100.0)	295
By Phase I trial								
1321.1	47 (30.7)	27 (77.1)	12 (17.1)	83 (77.6)	35 (27.1)	39 (37.1)	118 (50.0)	157
1321.2	46 (30.1)	0 (0.0)	46 (65.7)	0 (0.0)	46 (35.7)	46 (43.8)	46 (19.5)	46
1321.5	48 (31.4)	8 (22.9)	12 (17.1)	24 (22.4)	36 (27.9)	20 (19.0)	60 (25.4)	80
1321.6	12 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)	12 (9.3)	0 (0.0)	12 (5.1)	12

Subjects from the crossover trial 1321.2 are counted in more than 1 treatment group but only once in the overall column.

[1] All subjects in trial 1321.2 and some subjects in trials 1321.1 and 1321.5 were pre-treated with DE before infusion of idarucizumab/placebo.

Data source: data on file, analyses for RMP v1.0, Table 1.1.1.1; and Table 1.2.1: 1 in [c02344202-01] with 12 additional subjects in study 1321.6

Subgroup analyses by idarucizumab dose show that out of the 129 subjects treated with DE+Ida (DE pre-treatment) most subjects received doses between 1 g up to less than 2.5 g (38.8%), followed by subjects receiving 5 g (36.4%) and doses between 2.5 g up to less than 5 g (17.8%). Out of the 236 subjects treated with Ida/DE+Ida, most subjects received doses between 1 g up to less than 2.5 g (39.0%), followed by subjects receiving 2.5 g up to less than 5 g (19.9%) and 5 g (19.9%).

Analyses by treatment duration show that the majority of subjects received a single dose infusion (20 mg to 8000 mg): 72.1% DE+Ida and 84.7% Ida/DE+Ida. Further details are given in the following table.

SIII.Table 2 Phase I overall exposure to idarucizumab by dose - TS

	DE+Ida	**Ida/DE+Ida**
Total idarucizumab dose [g]	**Number of subjects N (%)**	**Number of subjects N (%)**
Total	129 (100.0)	236 (100.0)
Dose		
<1	--	23 (9.7)
≥1 to <2.5	50 (38.8)	92 (39.0)
≥2.5 to <5	23 (17.8)	47 (19.9)
=5	47 (36.4)	47 (19.9)
>5 to ≤8	9 (7.0)	27 (11.4)
Dosage		
Single dose (20 mg - 8000 mg)	93 (72.1)	200 (84.7)
Separated dosing 15 min (2.5 g + 2.5 g)	21 (16.3)	21 (8.9)
Separated dosing 60 min (5 g + 2.5 g)	9 (7.0)	9 (3.8)
Single dose 2.5 g + 2.5 g re-exposure after 60 days	6 (4.7)	6 (2.5)

Subjects from the crossover trial 1321.2 are counted in more than 1 treatment group.

Data source: 8-5-outputs-x1321csap-id-2018-005-2018-09-03, Tables 1.1.1.1 and 1.1.1.2 (studies 1321.1, 1321.2, 1321.5, 1321.6)

More than half of the subjects of the Phase I studies were male and aged between 19 and 44 years, in accordance with the inclusion criteria of the Phase I trials (1321.1 and 1321.5 contributed most of the subjects to the clinical programme and included only male subjects younger than 45 years). Similar proportions of idarucizumab-treated subjects (Ida/DE+Ida) were in the age categories of 45 to 64 years (11.4%) and 65 to 80 years (12.7%). Most of the female subjects were aged between 65 to 80 years. Further detail is given in the table below.

SIII.Table 3 Phase I overall exposure to idarucizumab by age and gender - TS

	Idarucizumab		Placebo	
	DE+Ida	**Ida/ DE+Ida**	**DE+placebo**	**Placebo/ DE+placebo**
***Gender/* age group [years]**	**Number of subjects N (%)**	**Number of subjects N (%)**	**Number of subjects N (%)**	**Number of subjects N (%)**
Total	129 (100.0)	236 (100.0)	70 (100.0)	105 (100.0)
Male				
19 – 44	72 (55.8)	173 (73.3)	23 (32.9)	56 (53.3)
45 – 64	15 (11.6)	21 (8.9)	11 (15.7)	13 (12.4)
65 – 80	17 (13.2)	17 (7.2)	17 (24.3)	17 (16.2)
Female				
19 – 44	6 (4.7)	6 (2.5)	0 (0.0)	0 (0.0)
45 – 64	6 (4.7)	6 (2.5)	6 (8.6)	6 (5.7)
65 – 80	13 (10.1)	13 (5.5)	13 (18.6)	13 (12.4)
Total				
19 – 44	78 (60.5)	179 (75.8)	23 (32.9)	56 (53.3)
45 – 64	21 (16.3)	27 (11.4)	17 (24.3)	19 (18.1)
65 – 80	30 (23.3)	30 (12.7)	30 (42.9)	30 (28.6)

No subjects >80 years or <18 years were enrolled in the Phase I studies (1321.1, 1321.2, 1321.5, 1321.6).
Subjects from the crossover trial 1321.2 are counted in more than 1 treatment group.

Data source: 8-5-outputs-x1321csap-id-2018-005-2018-09-03, Table 1.1.1.3

The majority of subjects in the Ida/DE+Ida and placebo/DE+placebo groups were White, comprising subjects from trials 1321.1 and 1321.2. Japanese and Chinese subjects from trials 1321.5 and 1321.6, respectively, contributed with about one third to the overall population.

In line with the inclusion criteria, most subjects treated with idarucizumab or placebo had a BMI of less than 25 kg/m^2. About one third of all subjects treated with idarucizumab or placebo had a BMI between ≥25 to <30 kg/m^2.

At baseline, all subjects in the combined Phase I studies had ALT/AST values within the normal reference range except 1 subject treated with idarucizumab who had ALT/AST values between 1x ULN to <2x ULN.

Nearly all subjects had normal bilirubin levels at baseline (96.2% Ida/DE+Ida, 98.1% placebo/DE+placebo). Of the idarucizumab-treated subjects (Ida/DE+Ida), 3.4% of subjects had elevated levels of bilirubin between 1x ULN to <2x ULN at baseline and 0.4% of subjects had bilirubin levels of ≥2x ULN to <3x ULN. Of the placebo-treated subjects (placebo/DE+placebo), 1.9% subjects had elevated bilirubin levels between 1x ULN to <2x ULN at baseline. Further detail is given in the table below.

SIII.Table 4 Phase I overall exposure to idarucizumab by subgroups - TS

	Idarucizumab		Placebo	
	DE+Ida	**Ida/ DE+Ida**	**DE+ placebo**	**Placebo/ DE+placebo**
	Number of subjects N (%)	**Number of subjects N (%)**	**Number of subjects N (%)**	**Number of subjects N (%)**
Total	129 (100.0)	236 (100.0)	70 (100.0)	105 (100.0)
Race				
American Indian or Alaska Native	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Asian	49 (38.0)	73 (30.9)	13 (18.6)	22 (21.0)
Black or African American	1 (0.8)	2 (0.8)	1 (1.4)	1 (1.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	79 (61.2)	160 (67.8)	56 (80.0)	82 (78.1)
BMI [kg/m^2]				
<25	87 (67.4)	159 (67.4)	34 (48.6)	65 (61.9)
≥25 to <30	39 (30.2)	74 (31.4)	33 (47.1)	37 (35.2)
≥30 to <35	3 (2.3)	3 (1.3)	3 (4.3)	3 (2.9)
≥35	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic function (ALT/AST) at baseline				
Normal	129 (100.0)	235 (99.6)	70 (100.0)	105 (100.0)
1x ULN to <2x ULN	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
≥2x ULN to <3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin at baseline				
Normal	121 (93.8)	227 (96.2)	69 (98.6)	103 (98.1)
1x ULN to <2x ULN	7 (5.4)	8 (3.4)	1 (1.4)	2 (1.9)
≥2x ULN to <3x ULN	1 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)
≥3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine clearance [mL/min][1] at baseline				
<30 (severe)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥30 to <50 (moderate)	1 (0.8)	1 (0.4)	1 (1.4)	1 (1.0)
≥50 to <80 (mild)	20 (15.5)	20 (8.5)	18 (25.7)	18 (17.1)
≥80 (normal)	108 (83.7)	215 (91.1)	51 (72.9)	86 (81.9)

[1] Based on the Cockcroft-Gault formula.

Subjects from the crossover trial 1321.2 are counted in more than 1 treatment group.

Data source: 8-5-outputs-x1321csap-id-2018-005-2018-09-03, Tables 1.1.1.4 and 1.1.1.5 (studies 1321.1, 1321.2, 1321.5, 1321.6)

SIII.2 CLINICAL TRIAL EXPOSURE IN PHASE III TRIALS IN PATIENTS

Overall, 503 patients were treated in the completed Phase III trial 1321.3 (REVERSE-AD). Of these, 301 patients had uncontrolled or life-threatening bleeding at study entry and were included in Group A, and 202 patients required surgery or other emergency procedure and were included in Group B. Relatively equal proportions (approximately 73%) of the patients in both groups completed the planned 90 day observation period. A total of 135 patients, 79 (26.2%) patients in Group A and 56 (27.7%) patients in Group B prematurely discontinued the planned, 90-day observation period. Of the 135 patients who did not complete the 90-day study period, 101 died.

The patient population included more men than women (54.5% and 45.5%, respectively). The median (range) age of all patients was 78.0 years (21.0 to 96.0 years); less than 10% of the population was younger than 65 years, and approximately 23% were aged 85 years and older. Further detail regarding sex, age, and age group is given in the table below.

SIII.Table 5 Phase III overall exposure to idarucizumab by baseline demographics (sex, age, and age group) - TS

	Group A	Group B	Total
Number of patients [N (%)]	301 (100.0)	202 (100.0)	503 (100.0)
Sex [N (%)]			
Male	172 (57.1)	102 (50.5)	274 (54.5)
Female	129 (42.9)	100 (49.5)	229 (45.5)
Age (years)			
Mean	77.1	75.9	76.6
SD	10.4	10.5	10.5
Min	24.0	21.0	21.0
Median	79.0	77.0	78.0
Max	96.0	96.0	96.0
Age group (years) [N (%)]			
<65 years	27 (9.0)	22 (10.9)	49 (9.7)
≥65 to <75 years	78 (25.9)	58 (28.7)	136 (27.0)
≥75 to <85 years	122 (40.5)	83 (41.1)	205 (40.8)
≥85 years	74 (24.6)	39 (19.3)	113 (22.5)

Group A = dabigatran etexilate-treated patients with life-threatening or uncontrolled bleeding
Group B = dabigatran etexilate-treated patients requiring emergency surgery or procedures for other morbidities
Groups A and B are not randomised groups.

Data source: clinical trial report 1321.3 [c12723965-01], Table 15.1.3: 1

The majority of patients were white (82.3%). Further detail regarding race and region is given in the table below.

SIII.Table 6 Phase III overall exposure to idarucizumab by baseline demographics (race and region) - TS

	Group A	Group B	Total
Number of patients [N (%)]	301 (100.0)	202 (100.0)	503 (100.0)
Race [N (%)]			
American Indian/Alaska Native	1 (0.3)	0 (0.0)	1 (0.2)
Asian	29 (9.6)	8 (4.0)	37 (7.4)
Black/African American	4 (1.3)	0 (0.0)	4 (0.8)
Hawaiian/Pacific Islander	16 (5.3)	14 (6.9)	30 (6.0)
White	239 (79.4)	175 (86.6)	414 (82.3)
Missing	12 (4.0)	5 (2.5)	17 (3.4)
Region [N (%)]			
Europe	127 (42.2)	98 (48.5)	225 (44.7)
North America	47 (15.6)	17 (8.4)	64 (12.7)
Asia	27 (9.0)	4 (2.0)	31 (6.2)
Latin America	2 (0.7)	4 (2.0)	6 (1.2)
Australia-New Zealand	87 (28.9)	69 (34.2)	156 (31.0)
Other	11 (3.7)	10 (5.0)	21 (4.2)

Group A = dabigatran etexilate-treated patients with life-threatening or uncontrolled bleeding
Group B = dabigatran etexilate-treated patients requiring emergency surgery or procedures for other morbidities
Groups A and B are not randomised groups.

Data source: clinical trial report 1321.3 [c12723965-01], Table 15.1.3: 1

The majority of patients had renal impairment at the time of enrolment (see table below).

SIII.Table 7 Phase III overall exposure to idarucizumab by baseline demographics (renal and hepatic function) - TS

	Group A	Group B	Total
Number of patients [N (%)]	301 (100.0)	202 (100.0)	503 (100.0)
Creatinine clearance [mL/min][1]			
N	292	197	489
Mean	57.4	61.7	59.1
SD	33.5	35.7	34.4
Min	6.1	7.9	6.1
Median	50.8	56.0	52.6
Max	216.9	198.7	216.9

SIII.Table 7 (cont'd) Phase III overall exposure to idarucizumab by baseline demographics (renal and hepatic function) - TS

	Group A	Group B	Total
Creatinine clearance [mL/min][1] [N (%)]			
<30 mL/min (severe renal impairment)	53 (17.6)	38 (18.8)	91 (18.1)
≥30 to <50 (moderate renal impairment)	86 (28.6)	41 (20.3)	127 (25.2)
≥50 to <80 (mild renal impairment)	95 (31.6)	68 (33.7)	163 (32.4)
≥80 (normal renal function)	58 (19.3)	50 (24.8)	108 (21.5)
Missing	9 (3.0)	5 (2.5)	14 (2.8)
Total bilirubin [N (%)]			
1×ULN to <2×ULN	52 (17.3)	26 (12.9)	78 (15.5)
≥2×ULN to <3×ULN	2 (0.7)	7 (3.5)	9 (1.8)
≥3×ULN	1 (0.3)	7 (3.5)	8 (1.6)
Normal	209 (69.4)	139 (68.8)	348 (69.2)
Missing	37 (12.3)	23 (11.4)	60 (11.9)
ALT/AST [N (%)]			
1×ULN to <2×ULN	25 (8.3)	21 (10.4)	46 (9.1)
≥2×ULN to <3×ULN	4 (1.3)	5 (2.5)	9 (1.8)
≥3×ULN	8 (2.7)	22 (10.9)	30 (6.0)
Normal	240 (79.7)	135 (66.8)	375 (74.6)
Missing	24 (8.0)	19 (9.4)	43 (8.5)

Group A = dabigatran etexilate-treated patients with life-threatening or uncontrolled bleeding
Group B = dabigatran etexilate-treated patients requiring emergency surgery or procedures for other morbidities
Groups A and B are not randomised groups.

[1] Based on the Cockroft−Gault formula.

Data source: clinical trial report 1321.3 [c12723965-01], Table 15.1.3: 1

At study entry, 311 (61.8%) patients were on a twice-daily dose of 110 mg dabigatran etexilate and 151 (30.0%) patients were on a twice-daily dose of 150 mg dabigatran etexilate. The primary reason for dabigatran use was stroke prevention in patients with atrial fibrillation, cited for 478 (95.0%) patients. The majority of patients had taken their last dose of dabigatran less than 24 hours before receiving their first vial of idarucizumab (median time of approximately 14.58 hours and 17.95 hours for Groups A and B, respectively).

8 patients received more than 1 dose of 5 g idarucizumab due to re-bleeding, a second emergency surgical procedure, and/or a bleeding after an emergency surgical procedure. In addition, another patient received 10 g idarucizumab as a result of a dosing error.

The high values of clotting tests and unbound sum dabigatran levels at baseline suggest that these patients required more than 5 g of idarucizumab for sustained reversal. As expected, severe renal impairment is a possible risk factor for elevated levels of dabigatran at baseline as well as for re-occurrence of dabigatran anticoagulation after idarucizumab treatment. The

treating physician may consider monitoring the clinical condition of such patients. In case of a second intervention or recurrent bleeding and prolonged clotting times, a second dose of idarucizumab may be considered.

In both groups, the majority of patients had a daily dose of 110 mg bid dabigatran (61.5% group A and 62.4% group B), most patients were reported in the SPAF indication (95.7% group A and 94.1% group B), and most patients were reported with time since last DE intake of ≥12 hours and <24 hours (38.5% group A and 32.7% group B). Among the 301 treated patients in Group A, the most common qualifying bleeding events were gastrointestinal bleeding (45.5%), ICH (32.6%), and "other" (17.3%). Approximately 25.9% of the patients in Group A had bleeding due to trauma [c12723965-01, section 10.4.4]. Further detail is given in the table below.

SIII.Table 8 Phase III overall exposure to idarucizumab by baseline conditions and relevant medical history - TS

	Group A		**Group B**		**Total**	
Number of patients [N (%)]	301	(100.0)	202	(100.0)	503	(100.0)
Daily dose of dabigatran [N (%)]						
75 mg bid	16	(5.3)	8	(4.0)	24	(4.8)
110 mg bid	185	(61.5)	126	(62.4)	311	(61.8)
150 mg bid	94	(31.2)	57	(28.2)	151	(30.0)
Other	3	(1.0)	11	(5.4)	14	(2.8)
Dabigatran indication [N (%)]						
Atrial fibrillation	288	(95.7)	190	(94.1)	478	(95.0)
Orthopaedic surgery	0	(0.0)	3	(1.5)	3	(0.6)
VTE	5	(1.7)	4	(2.0)	9	(1.8)
Other	8	(2.7)	5	(2.5)	13	(2.6)
Time since last dabigatran intake (hours)[a]						
N	299		202		501	
Mean	17.74		22.35		19.60	
SD	12.71		17.36		14.91	
Min	1.47		2.58		1.47	
Median	14.58		17.95		15.55	
Max	90.42		105.77		105.77	

SIII.Table 8 (cont'd) Phase III overall exposure to idarucizumab by baseline conditions and relevant medical history - TS

	Group A		Group B		Total	
Time since last dabigatran intake [N (%)]						
<12 hours	114	(37.9)	65	(32.2)	179	(35.6)
12≤ and <24 hours	116	(38.5)	66	(32.7)	182	(36.2)
24≤ and <48 hours	60	(19.9)	56	(27.7)	116	(23.1)
≥48 hours	9	(3.0)	15	(7.4)	24	(4.8)
Unknown	2	(0.7)	0	(0.0)	2	(0.4)

Max = maximum; min = minimum; SD = standard deviation; VTE = venous thrombotic events
[a] Computed as (date/time of first idarucizumab administration − date/time of last dabigatran dose). Partial last dabigatran administration date/time was imputed as midnight of the day of last intake.
Groups A and B are not randomised groups.
Data source: clinical trial report 1321.3 [c12723965-01], Table 15.1.3: 2

SIII.3 REFERENCES

SIII.3.1 Published references

Not applicable

SIII.3.2 Unpublished references

c02344202-01 Summary of clinical safety. Idarucizumab. 29 Jan 2015

c12723965-01 A Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous 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 (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial. Idarucizumab. 1321.3. 07 Apr 2017

ABBREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
DE	Dabigatran etexilate
ICH	Intracerebral haemorrhage
Ida	Idarucizumab
Max.	Maximum
Min.	Minimum
RMP	Risk management plan
SD	Standard deviation
SPAF	Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
TS	Treated set
ULN	Upper limit of normal
VTE	Venous thrombolic event

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

Hypersensitivity to the active substance or any of its excipients	
Reason for exclusion:	Patients with known hypersensitivity reactions to the active substance or to any of the excipients are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients.
Is it considered to be included as missing information?	No
Rationale:	Known hypersensitivity cannot be considered as missing information. Hypersensitivity to the active substance or to any of the excipients is covered in the SmPC ("Special Warnings and Precaution").
Hereditary fructose intolerance	
Reason for exclusion:	Praxbind contains sorbitol as excipient (4 g sorbitol per dose). Patients with HFI will react to sorbitol.
Is it considered to be included as missing information?	No
Rationale:	HFI is covered in the SmPC in the way that in patients with HFI, the risk of treatment with Praxbind must be weighed against the potential benefit of such an emergency treatment and that if Praxbind is administered in these patients, intensified medical care during Praxbind exposure and within 24 hours of exposure is required. Furthermore, in section "Special Warnings and Precautions" it is mentioned that in case of HFI, the substance sorbitol contained in Praxbind may cause serious adverse reactions.
Paediatric patients	
Reason for exclusion:	Standard exclusion criterion for clinical trials at the beginning of the clinical development
Is it considered to be included as missing information?	Yes

Paediatric patients (cont'd)	
Rationale:	A paediatric investigational plan including a deferral (EMEA-001438-PIP01-13-M01) was granted by the EMA. The paediatric clinical development is ongoing and the benefit-risk profile of Praxbind for paediatric patients has not yet been established. Therefore, this topic is considered missing information.
Pregnant or breast-feeding women	
Reason for exclusion:	Clinical trials in pregnant or breast-feeding women cannot be conducted for ethical reasons.
Is it considered to be included as missing information?	Yes
Rationale:	Very limited experience is available from clinical trial and post-marketing data. The risk for the unborn or breastfed child is not known, but cannot be excluded. Therefore, this topic is considered missing information.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency (the only relevant events may be related to immunogenicity several months after Praxbind treatment.), or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**	
	Number	**Person-time**
Pregnant women	Not included in the clinical development programme	Not applicable*
Breast-feeding women	Not included in the clinical development programme	Not applicable*

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure	
	Number	Person-time
Patients with relevant comorbidities:		Not applicable*
• Patients with hepatic impairment	See SIII.Tables 4, 7	Not applicable*
• Patients with renal impairment	See SIII.Tables 4, 7	Not applicable*
• Patients with cardiovascular impairment	302 patients in clinical trial 1321.3 [c12723965-01], Table 15.1.3: 6	Not applicable*
• Immuno-compromised patients	Not known	Not applicable*
• Patients with a disease severity different from inclusion criteria in clinical trials	Not known	Not applicable*
Population with relevant different ethnic origin	See SIII.Tables 4, 6	Not applicable*
Subpopulations carrying relevant genetic polymorphisms	Not known	Not applicable*
Other	Not applicable	Not applicable*

* The recommended dose of idarucizumab is 5.0 g (2 x 2.5 g); therefore, providing a person-time is not applicable.

Data source: SIII.1, SIII.2

SIV.4 REFERENCES

SIV.4.1 Published references

Not applicable

SIV.4.2 Unpublished references

c12723965-01 A Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous 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 (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial. Idarucizumab. 1321.3. 07 Apr 2017

ABBREVIATIONS

EMA	European Medicines Agency
HFI	Hereditary fructose intolerance
RMP	Risk management plan
SmPC	Summary of product characteristics

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

Ex-factory (commercial) sales numbers for idarucizumab as the basis for the estimation of the post-authorisation (non-clinical trial) exposure are only available for complete months, from the beginning of October 2015 to the end of September 2019.

The method used to estimate the patient exposure to the marketed drug is based on the number of bulk units (mL) sold (ex-factory sales). It is assumed that all bulk units were used by the patients and that each patient was treated with 100 mL (2 vials with 50 mL each, i.e. the recommended daily dose). The number of patients treated is calculated by dividing the bulk units (mL) sold (ex-factory sales) by the defined daily dose.

SV.1.2 Exposure

The cumulative patient exposure to marketed idarucizumab is estimated to be 54 113 exposed patients (October 2015 to September 2019).

Exposure data from marketing experience by age, gender, or indications are not available for idarucizumab. As there is only 1 dose and formulation for idarucizumab, a presentation by these variables is not applicable. The cumulative exposure data for idarucizumab from marketing experience is presented by region/country in the table below.

SV.Table 1 Cumulative exposure from marketing experience by region/country for idarucizumab (October 2015 to September 2019)

Region/country	Units sold [1] [mL]	Exposed patients [n] [1]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[1] All numbers are rounded to the nearest integer.

Data source: Praxbind PBRER, DLP 15 Oct 2019 [s00083883-01], Table 4

SV.2 REFERENCES

SV.2.1 Published references

Not applicable

SV.2.2 Unpublished references

s00083883-01 Periodic benefit risk evaluation report. Idarucizumab. 16 Oct 2018 to 15 Oct 2019. 21 Nov 2019.

ABBREVIATIONS

EEA	European Economic Area
EU	European Union
USA	United States of America

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Idarucizumab is available as prescription medicine only and is administered in a hospital setting by trained medical personal only. Pharmacological properties, non-clinical, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic, or mood-elevating effects; or other effects that might lead to dependency. Abuse for illegal purpose is not expected with idarucizumab.

SVI.2 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Since this is not an initial RMP submission, only an overview of the safety concerns identified at the time of first authorisation is provided below.

SVIII.Table 1 Summary of safety concerns at the time of first marketing authorisation

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

Data source: Praxbind RMP version 1.0 [s00018805-01], SVIII.Table 1

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Since the last update, there are no new or reclassified safety concerns.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The evaluation of safety is based on the treated set of patients, i.e. representing all patients who received trial medication. For the evaluation of important risks, data from the completed phase III trial 1321.3 were analysed (final analysis, DLP 18 Nov 2016 [c12723965-01]). This open-label, uncontrolled, cases series clinical trial comprises 2 non-randomised patient groups:

- Group A: dabigatran etexilate-treated patients with life-threatening or uncontrolled bleeding
- Group B: dabigatran etexilate-treated patients requiring emergency surgery or procedures for other morbidities

All AEs with an onset date/time after the first vial of trial medication up to 5 days after the last intake of trial medication were assigned to the treatment period for evaluation. In addition, AEs with an onset date before the start of the trial treatment but with worsening in

intensity during the treatment were also assigned to the on-treatment period. AEs were coded using MedDRA version 19.1 (valid at the time of the analysis).

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risks

None

SVII.3.1.2 Important potential risk: Hypersensitivity

SVII.3.1.2.1 Potential mechanisms

Idarucizumab is a humanised monoclonal antibody fragment derived from an Immunoglobulin G1 subclass isotype molecule. The presence of modified proteins in the human blood may result in a certain risk for the occurrence of allergic reactions.

SVII.3.1.2.2 Evidence source and strength of evidence

There is a general risk from proteins to cause hypersensitivity reactions. In idarucizumab, however, the fc fragment (responsible for hypersensitivity reactions in general) is missing. Furthermore, the antibody is humanised. Thus, the risk for hypersensitivity reactions in patients treated with Praxbind is rather low.

Based on the results from the phase III trial 1321.3 and in line with data from spontaneous reporting, there were no facts or evidence that events of hypersensitivity were related to idarucizumab treatment. Therefore, there is no need for risk minimisation measures for the important potential risk ‘hypersensitivity’.

However, following the completed EU variation (procedure EMEA/H/C/003986/II/0007) to include hypersensitivity as important potential risk in the RMP, the MAH updated the EU RMP to version 3.1 (dated 26 Sep 2017) [s00018805-05] and retains this safety concern as an important potential risk also in this updated RMP version 4.0.

The position of the MAH remains that hypersensitivity does not meet the criteria of an important potential risk.

SVII.3.1.2.3 Characterisation of the risk

Clinical trial data

The potential for idarucizumab to cause hypersensitivity AEs was screened in all 503 patients enrolled in the phase III trial 1321.3. Hypersensitivity events were identified by applying the narrow SMQ ‘Hypersensitivity’. This query resulted in the identification of 58 (11.5%) patients (29 [9.6%] of 301 patients enrolled in Group A and 29 [14.4%] of 202 patients enrolled in Group B) with AEs that theoretically could be associated with a hypersensitivity reaction to idarucizumab during the entire 90-day trial period [c12723965-01].

35 (60%) of the 58 patients experienced the event in the on-treatment period (0-5 days) and the remaining 23 (40%) patients experienced the event in the follow-up treatment period (6-90 days).

Idarucizumab is administered as a single dose treatment in patients who need rapid reversal of the dabigatran anticoagulant effect. The half-life time for idarucizumab is approximately 45 minutes. Taking this into consideration, the focus of the idarucizumab safety evaluation is the 5-day on-treatment period.

Of the aforementioned 35 patients (on-treatment period), 21 were in Group A and 14 were in Group B. All 35 patients with potential hypersensitivity reactions onset in the on-treatment period were reviewed on a case-by-case basis. All relevant conditions and concomitant medications were considered in a further analysis of these 35 patients.

On single-case level, for all identified hypersensitivity reactions, strong confounders could be identified which were assessed more likely to have caused the event. In 23 of the 35 patients, concomitant medications such as antibiotics or analgesics have been identified as explanations that are more plausible. The remaining 12 case reports identified by the narrow SMQ 'Hypersensitivity' were not associated to hypersensitivity events but to other conditions such as worsening of comorbidities (e.g. chronic obstructive pulmonary disease, congestive heart failure), signs and symptoms of underlying conditions (e.g. thorax trauma after motor vehicle accident, haemodynamic failure due to extensive abdominal ischaemia) or infectious diseases (e.g. pneumonia). 14 of the 35 cases were reported as serious, 5 with a fatal outcome (none related to hypersensitivity). In only 2 of the 35 patients, the investigator assessed the event as related to idarucizumab treatment. Narrative summaries for both of these patients are provided below.

1 of the 2 aforementioned patients, a 77-year-old female, was treated with idarucizumab for a large intracranial haemorrhage. Immediately after administration of the first vial of the trial medication, the patient experienced vomiting, deterioration of consciousness from mild drowsy to coma, and blood pressure decreased from 130-140/70-77 to 69/44 mmHg. The events were reported as 'anaphylactic reaction'. After administration of norepinephrine, the patient's blood pressure was stabilised. Approximately 19 hours after idarucizumab treatment, the patient experienced hypotension, rash, and itching; these events disappeared after stopping parenteral nutrition and after administration of antihistamine treatment. The day following idarucizumab treatment, parenteral nutrition was administered again and the patient experienced urticaria and rash.

As an alternative explanation of the AEs, the investigator also considered a seizure disorder based on the left-sided gaze deviation and slight tonic murmur (suspicious) of the extremities.

> *BI assessment:* The symptoms reported in close temporal relationship with the application of idarucizumab, including the hypotensive reaction, are compatible with increased intracranial pressure, and thus are most likely caused by the severity of the intracranial haemorrhage; the suspected diagnosis of 'anaphylactic reaction' appears

to be questionable. The hypersensitivity reactions reported later on (after 19 hours and on the following day) are associated with the administration of parenteral nutrition; for these hypersensitivity reactions, a positive de- and re-challenge with parenteral nutrition was reported.

The other of the 2 aforementioned patients, a 48-year-old male, was treated with idarucizumab for intracranial haemorrhage. 2 days after idarucizumab treatment, the patient experienced a rash. As relevant concomitant medications on the day of idarucizumab treatment, tramadol and ondansetron were initiated and both treatments were ongoing at the time of occurrence of the rash. Additionally, on the day of event onset, dabigatran etexilate was re-initiated.

BI assessment: At onset of the rash, the patient concomitantly received tramadol, ondansetron, and dabigatran etexilate; all 3 drugs are known to cause a hypersensitivity reaction. Therefore, it is considered more likely that one of these drugs has caused the event.

In conclusion, in 2 of the reported hypersensitivity events did the investigator assess the event as related to idarucizumab. However, for both patients, strong confounders were reported, which were more likely to have caused the event. In general, for all patients with hypersensitivity events identified by the narrow SMQ 'Hypersensitivity', no facts or evidence could be found that these events were related to idarucizumab treatment. The data evaluated did not identify any event, which qualified for an adverse drug reaction for idarucizumab.

Post-marketing data

No hypersensitivity reactions related to Praxbind were identified in post-marketing data.

SVII.3.1.2.4 Risk factors and risk groups

Risk groups or risk factors are unknown.

SVII.3.1.2.5 Preventability

The preventability is unknown.

SVII.3.1.2.6 Impact on the risk-benefit balance of the product

There is a theoretical risk of a hypersensitivity reaction to idarucizumab. Patients treated with Praxbind are under intensive care unit conditions and possible hypersensitivity reactions can be treated immediately.

Currently, hypersensitivity is considered to have no impact on the risk-benefit balance of the product.

SVII.3.1.2.7 Public health impact

No impact on public health is expected.

SVII.3.1.3 Important potential risk: Immunogenicity

SVII.3.1.3.1 Potential mechanisms

Treatment with idarucizumab may lead to an anti-drug-antibody response in the concerned patient. Antibodies against idarucizumab and/or dabigatran may be the result.

SVII.3.1.3.2 Evidence source and strength of evidence

Based on the results from the phase III trial 1321.3 and in line with data from spontaneous reporting, there were no facts or evidence that events of immunogenicity were related to idarucizumab treatment. Therefore, there is no need for risk minimisation measures for the important potential risk 'immunogenicity'.

However, following the completed EU variation (procedure EMEA/H/C/003986/II/0007) to include immunogenicity as important potential risk in the RMP, the MAH updated the EU RMP to version 3.1 (dated 26 Sep 2017) [s00018805-05] and retains this safety concern as an important potential risk also in this updated RMP version 4.0.

The position of the MAH remains that immunogenicity does not meet the criteria of an important potential risk.

SVII.3.1.3.3 Characterisation of the risk

Clinical trial data

Immunogenicity based on formation of ADAs is a Type III hypersensitivity reaction, which is described clinically as serum sickness. To assess possible ADA-based immune response to idarucizumab treatment, the AE data in the phase III trial 1321.3 were scanned for the MedDRA LLT 'Fever', since this is a hallmark symptom of serum sickness [c12723965-01].

In addition, in all patients identified with the LLT 'Fever', also further symptoms known for serum sickness such as 'general ill feeling', 'hives', 'itching', 'joint pain', and 'rash' have been looked for and considered. For the evaluation, also the temporal relationship between idarucizumab administration and occurrence of the events has been assessed.

32 patients with fever (of 503 entered, 6%) were identified and these were further selected if they had at least 1 positive ADA sample.

None of the 32 patients with fever was positive for ADA at baseline. In the majority of the 32 patients, "fever" was assessed as a symptom of infectious diseases or of the underlying condition (e.g. post-surgery fever).

In 3 of the 32 patients, treatment-emergent ADAs were detected:

- Patient 1: ADAs were positive at visits 5 and 6 (30 and 90 days after application of idarucizumab). The patient experienced a 2-day fever episode 5 days after

idarucizumab treatment. The event was judged as unrelated. The patient had been on paracetamol at the time of trial entry and continued until 7 days post-treatment.
- Patient 2: ADAs were positive at visit 5 (30 days after application of idarucizumab). The patient experienced fever 44 days after idarucizumab treatment. As a confounder for fever a hepatic abscess (time to onset same as for fever) has been reported.
- Patient 3: ADAs were positive at visit 5 (30 days after application of idarucizumab). Fever occurred 8 days after idarucizumab treatment. As a confounder worsening of pleural effusion (time to onset same as fever) has been reported.

The likelihood for a serum disease in all 3 patients is very low; the reported confounders seem to be more likely to have caused the fever or the transient fever episode of 2 days seems to be short for confirming a serum sickness diagnosis.

For 10 of the 32 patients with fever, plasma sampling for ADA assessment was done only at baseline (all were negative). No on-treatment samples were available and the clinical pictures for these 10 patients were evaluated as follows:

- In 3 patients, infectious diseases (urinary tract infection, aspiration pneumonia, and candidiasis) have been reported as explanations for fever.
- In further 5 patients, other confounders such as febrile post-operative reaction (1 patient) and bleeding (intracranial haemorrhage, resorption of haematoma, haematuria, and not further specified bleeding [4 patients]) have been reported as explanations for fever.
- In only 2 further patients, no confounders associated with the fever episode have been reported:
    - 1 patient did not receive treatment for the fever episode (which occurred at day 12) and recovered 2 days after onset of the event.
    - The other patient of these 2 patients experienced fever (37.7°C) at day 8 and recovered 3 days after onset of the event.

Anti-idarucizumab antibodies occurred with a low frequency in this population, 28 of 501 (5.6%) patients tested positive for ADAs at any time during the trial. Of these, ADAs in 19 patients (3.8%) were pre-existing and most of the ADAs were non-specific. Only 1.8% (9 patients) had treatment-emergent ADAs. The titres of anti-idarucizumab antibodies in positive samples were generally low (the highest observed titre of 64 occurred at baseline). Based on the available data, the likelihood of ADA-based immunogenicity in patients receiving a single 5 g dose of idarucizumab is very low [c12723965-01].

To get a sense of the highest equivalent concentration of anti-idarucizumab antibodies in any of the positive tested subjects, it was calculated that the amount of anti-idarucizumab antibodies in the subject's circulation associated with a titre of 64 would be roughly 16 mg. For the proposed 5 g therapeutic dose of idarucizumab, it is clear that this dose is overwhelming in comparison to the estimated maximum concentration of treatment-emergent anti-idarucizumab antibodies observed to-date (5000 mg versus 16 mg). 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 at a later point in time [c02344198-01].

Post-marketing data

No immunogenicity related to Praxbind was identified in post-marketing data.

SVII.3.1.3.4 Risk factors and risk groups

Risk groups or risk factors are unknown.

SVII.3.1.3.5 Preventability

The preventability is unknown.

SVII.3.1.3.6 Impact on the risk-benefit balance of the product

Formation of monoclonal anti-idarucizumab antibody

Given the roughly 3000 mL plasma volume of a 70 kg person, the amount of anti-idarucizumab antibody in circulation of a subject with an ADA titre of 40 calculates to roughly 10 mg (equivalent amount based on activity of a positive control). By comparison, the proposed 5 g therapeutic dose of idarucizumab is 500-fold greater. 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. By this analysis, it hardly matters whether the ADA are neutralising.

Formation of antibodies against dabigatran

Taking into account the possible amount of an anti-dabigatran antibody, it is considered that there might only be a theoretical impact of the antibody in the very initial treatment phase after the re-initiation of dabigatran etexilate.

In conclusion, immunogenicity is considered to have only little impact on patients treated with idarucizumab.

SVII.3.1.3.7 Public health impact

No impact on public health is expected.

SVII.3.1.4 Important potential risk: Thrombotic events

SVII.3.1.4.1 Potential mechanisms

Genuine risk of underlying conditions such as comorbidities and other risk factors

SVII.3.1.4.2 Evidence source and strength of evidence

Based on the results from the phase III trial 1321.3 and in line with data from spontaneous reporting, there were no facts or evidence that thrombotic events were related to idarucizumab treatment. Therefore, there is no need for risk minimisation measures for the important potential risk 'thrombotic events'.

However, following the completed EU variation (procedure EMEA/H/C/003986/II/0007) to include thrombotic events as important potential risk in the RMP, the MAH updated the EU RMP to version 3.1 (dated 26 Sep 2017) [s00018805-05] and retains this safety concern as an important potential risk also in this updated RMP version 4.0.

The position of the MAH remains that thrombotic events do not meet the criteria of an important potential risk.

SVII.3.1.4.3 Characterisation of the risk

Clinical trial data

Patients receiving anticoagulant therapy have underlying disease states that predispose them to thrombotic events. Treatment with a reversal agent such as idarucizumab exposes the patient to the thrombotic risk of their underlying disease. In the phase III trial 1321.3 [c12723965-01], possible protocol-specified thrombotic events were retrieved from the clinical trial database. The relevant medical conditions and the MedDRA terms used are shown below:

- Ischaemic stroke: narrow SMQ 'Ischaemic central nervous system vascular conditions'
- MI: narrow SMQ 'Myocardial infarction'
- PE: MedDRA PTs Pulmonary embolism, Post-procedural pulmonary embolism, Obstetrical pulmonary embolism, Metastatic pulmonary embolism, Pulmonary infarction, SI QIII TIII pattern, Pulmonary endarterectomy
- DVT: narrow SMQ 'Embolic and thrombotic events, venous'
- Systemic embolism: MedDRA PTs Amaurosis fugax, Aortic embolus, Arterial bypass occlusion, Arterial occlusive disease, Basilar artery occlusion, Brachiocephalic artery occlusion, Carotid arterial embolus, Carotid artery occlusion, Cerebellar artery occlusion, Cerebral artery embolism, Cerebral artery occlusion, Coeliac artery occlusion, Coronary artery embolism, Coronary artery occlusion, Coronary artery reocclusion, Coronary vascular graft occlusion, Embolism arterial, Femoral artery embolism, Hepatic artery embolism, Hepatic artery occlusion, Iliac artery embolism, Iliac artery occlusion, Leriche syndrome, Mesenteric arterial occlusion, Mesenteric artery embolism, Penile artery occlusion, Peripheral arterial occlusive disease, Peripheral arterial reocclusion, Peripheral embolism, Precerebral artery occlusion, Renal artery occlusion, Renal embolism, Retinal artery embolism, Retinal artery occlusion, Spinal artery embolism, Splenic embolism, Subclavian artery embolism, Subclavian artery occlusion, Thromboembolectomy, Vertebral artery occlusion, Choroidal infarction, Embolism, Paradoxical embolism, Peripheral artery occlusion,

Mesenteric vascular occlusion, Microembolism, Hepatic infarction, Inner ear infarction, Intestinal infarction, Pancreatic infarction, Placental infarction, Renal infarct, Retinal infarction, Spinal cord infarction, Splenic infarction, Testicular infarction, Thyroid infarction, Pulmonary artery occlusion

Thrombotic events were subsequently adjudicated by an Endpoint Adjudication Committee.

The Endpoint Adjudication Committee evaluated AEs to define thrombotic events that took place at any time during the entire trial (90 days). 34 patients experienced at least 1 thrombotic event.

Adjudicated thrombotic events were reported for 11 patients within 5 days post-idarucizumab treatment (on treatment period) and for 5 patients from day 6 to day 10. The remaining events had occurred between 11 and 90 days post-idarucizumab treatment. 1 patient experienced an event of MI minutes before administration of the first vial of idarucizumab.

23 of the 34 patients who experienced at least 1 thrombotic event were not on any antithrombotic therapy at the time of onset of the event.

Among the 301 patients in Group A, there were 19 with thrombotic events (6.3%), which included 6 with ischemic stroke (2%), 4 with MI (1.3%), 3 with DVT (1%), 1 with PE (0.3%), 4 with DVT + PE (1.3%), and 1 with systemic embolism (0.3%).

Among the 202 patients in Group B, there were 15 with thrombotic events (7.4%), which included 3 with ischemic stroke (1.5%), 3 with MI (1.5%), 3 with DVT (1.5%), 4 with PE (2.0%), 1 with systemic embolism + DVT (0.5%), and 1 with systemic embolism (0.5%).

Post-marketing data

No increased risk for thrombotic events from the use of Praxbind was identified in post-marketing data.

SVII.3.1.4.4 Risk factors and risk groups

A risk group/factor is the generation of anti-dabigatran antibodies, potentially leading to a decrease of anticoagulant effect of dabigatran after its re-initiation.

Idarucizumab specifically reverses the anticoagulant effect of dabigatran. Idarucizumab does not have an impact on any factor of the coagulation cascade; therefore, without re-initiation of sufficient anticoagulant treatment, patients are at risk for thrombotic events associated with their underlying conditions such as comorbidities and other thrombotic risk factors, which had constituted the treatment indication for the initial therapy with dabigatran etexilate.

SVII.3.1.4.5 Preventability

Re-institution of dabigatran therapy or treatment with any other anticoagulant may be considered 24 hours after the last vial of idarucizumab and after normal haemostasis was achieved.

SVII.3.1.4.6 Impact on the risk-benefit balance of the product

Dependent on the underlying individual risk, the patient may experience thrombotic events with impact on any organs (e.g. brain, kidney, lung, etc.).

SVII.3.1.4.7 Public health impact

No public health impact is expected.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing information: Paediatric patients

SVII.3.2.1.1 Evidence source

A paediatric investigational plan including a deferral (EMEA-001438-PIP01-13-M01) was granted by the European Medicines Agency.

Cumulatively, there were 2 paediatric cases as of 15 Oct 2019:

- A 17-year-old female was enrolled in the paediatric Pradaxa trial 1160.108. The patient underwent surgery for venous malformation in the right lower limb. Post-surgery Pradaxa was initiated for thrombosis prophylaxis. The patient experienced a major post-procedural haemorrhage with the need for surgical intervention. The patient was enrolled in the Praxbind paediatric trial 1321.7 and was treated with 5 g Praxbind. Approximately 1 hour after Praxbind treatment, the bleeding had stopped. 1 day after Praxbind treatment, the patient experienced a mild and non-serious thrombocytopenia ($35x10^9$/L). The patient recovered without treatment. According to the investigator, there was no causal relationship between this event and Praxbind. No further events were reported in this case.

- Furthermore, post-marketing information on a 15-year-old female was received, using an overdose of Pradaxa for suicidal intention (prescribed to her father). This patient was treated with Praxbind, but not in the frame of paediatric trial 1321.7. The dabigatran plasma level prior to Praxbind treatment was 1974 mcg/L and after Praxbind application <30 mcg/L. No events related to Praxbind were reported.

A worldwide non-interventional chart review study (1321.11, “Safety of potential paediatric patients treated by idarucizumab: a worldwide non-interventional chart review study”) [c30045812-01] was conducted as part of the paediatric investigational plan. No conclusion can be drawn, as no paediatric patients receiving idarucizumab were enrolled into this non-interventional study. A study summary is provided in Appendix 7.

SVII.3.2.1.2 Anticipated risk/consequence of the missing information

Idarucizumab is studied in children (see previous section). Currently, the risk for the paediatric population when treated with idarucizumab is considered low.

SVII.3.2.2 Missing information: Pregnancy/breast-feeding

SVII.3.2.2.1 Evidence source

Idarucizumab has not been studied in pregnant or breast-feeding women. Reproductive and developmental toxicity studies have not been performed, given the nature and the intended clinical use of the medicinal product. Idarucizumab may be used during pregnancy, if the clinical benefit outweighs the potential risks. It is unknown if idarucizumab is excreted in human milk.

Cumulatively, no cases of pregnancy were reported as of 15 Oct 2019.

SVII.3.2.2.2 Anticipated risk/consequence of the missing information

A theoretical risk for the unborn or breast-fed child exists. Idarucizumab may be used during pregnancy, if the clinical benefit outweighs the potential risks. It is unknown if idarucizumab is excreted in human milk.

SVII.3.2.3 Missing information: Re-exposure to idarucizumab

SVII.3.2.3.1 Evidence source

Based on the profile of major bleeding in RE-LY, 10% to 15% of patients with a major bleeding experienced a second major bleeding during the course of the trial (mean duration 2.0 years). This suggests that some patients have the potential to be exposed to a second dose of idarucizumab months or years later. There is a theoretical risk of a hypersensitivity reaction or an immune response (see Section SVII.3.1.3) to idarucizumab. Patients treated with Praxbind are under intensive care unit conditions and possible hypersensitivity reactions can be treated immediately. There is a general risk from proteins to cause hypersensitivity reactions. In idarucizumab, however, the fc fragment (responsible for hypersensitivity reactions in general) is missing. Furthermore, the antibody is humanised. Thus, the risk for hypersensitivity reactions in patients treated with Praxbind is rather low.

Information on re-exposure to idarucizumab is available from trial 1321.2 [c02742738-02]. In this trial, idarucizumab was given as single infusion of 1 g, 2.5 g, and 5 g over 5 minutes or as 2 single infusions of each 2.5 g (1 hour apart) after pre-treatment with DE. Additionally, 9 subjects aged 45 to 64 years receiving 2.5 g idarucizumab were re-exposed to 2.5 g idarucizumab approximately 2 months after the second period of the trial was completed.
In the phase III trial 1321.3, 8 patients received more than 1 dose of 5 g idarucizumab due to re-bleeding, a second emergency surgical procedure, and/or a bleeding after an emergency surgical procedure [c12723965-01], Table 11.3.1: 1. All patients who received more than 1 dose of 5 g idarucizumab for reasons other than a dosing error (1 patient) were assigned an additional patient number for each additional dose to be able to record the data separately. It

is important to note that all patients received their additional doses during the same first period of hospitalisation.

All cases from post-marketing experience were followed-up for past Praxbind use. Out of the 132 case reports received in the reporting interval, in 13 cases, past Praxbind use was reported as ‘unknown’, in 9 cases as ‘no’, and for 109 patients, no information on past Praxbind use was provided. In the remaining case report, Praxbind was reported as past medication; this patient received a second dose of Praxbind 51 days after initial treatment due to a re-occurrence of a chronic subdural haematoma. In this patient, no further events were reported.

Cumulatively, from post-marketing experience, 4 patients were identified where Praxbind had been administered in the past. The period between both Praxbind treatments was 10 days to 51 days. In none of these 4 patients, events associated to immunogenicity were reported.

In summary, from clinical trials the MAH received 17 case reports of administration of a second Praxbind dose, in 8 cases from trial 1321.3 upon re-occurrence of bleeding or for secondary emergency surgery/procedure and in 9 volunteers in trial 1321.2. In addition, from post-marketing experience, 40 patients received a second Praxbind dose; however, in 36 of the 40 cases, Praxbind was administered during the same hospitalisation and in only 4 patients (described in the previous paragraph), Praxbind was a past medication. The 4 patients did not manifest any immunogenic events.

From clinical trial experience, the high values of clotting tests and unbound sum dabigatran levels at baseline suggest that patients required more than 5 g of idarucizumab for sustained reversal. As a consequence of the renal elimination, severe renal impairment is a possible risk factor for elevated levels of dabigatran at the start of reversal therapy with Praxbind, as well as for re-occurrence of dabigatran anticoagulation after idarucizumab treatment. The treating physician may consider monitoring the clinical condition of such patients. In case of a second intervention or recurrent bleeding and prolonged clotting times, a second dose of idarucizumab may be considered.

Presence of anti-idarucizumab antibodies and epitope specificity

Anti-idarucizumab antibodies occurred with a low frequency in this population treated in the phase III trail 1321.3, 28 of 501 (5.6%) patients tested positive for ADAs at any time during the study. Of these, ADAs in 19 patients (3.8%) were pre-existing and most of the ADAs were non-specific. Only 1.8% (9 patients) had treatment-emergent ADAs. The titres of anti-idarucizumab antibodies in positive samples were generally low. No impact on the effectiveness of treatment with idarucizumab was detected [c12723965-01].

Compared to phase I trials (12% of subjects) [c02344198-01], in the phase III trial 1321.3, the frequency of pre-existing antibodies with cross-reactivity to idarucizumab was lower (5.6% vs. 12%).

It appears to be a common finding that pre-existing antibodies can cause a positive result in anti-drug antibody assays. However, the impact of these antibodies on the efficacy and safety of a therapeutic drug is small [R13-2362].

Effect of pre-existing anti-idarucizumab antibodies on PK of idarucizumab

The titres of anti-idarucizumab antibodies in the positive samples were generally low. Pre-existing anti-idarucizumab antibodies had no apparent effect on the PK or PD of idarucizumab; individual plasma concentrations and coagulation times were generally within the 95th percentile of the overall population [c12723965-01].

SVII.3.2.3.2 Anticipated risk/consequence of the missing information

Re-exposure to idarucizumab can directly lead to hypersensitivity and can result in the creation of antibodies, which in turn may lead to lack of efficacy. However, patients treated with Praxbind are under intensive care unit conditions and possible hypersensitivity reactions can be treated immediately, should they occur.

SVII.4 REFERENCES

SVII.4.1 Published references

R13-2362 Xue L, Fiscella M, Rajadhyaksha M et al. Pre-existing biotherapeutic reactive antibodies: survey results within the American Association of Pharmaceutical Scientists. AAPS Journal, Online First, Published online: 26 Apr 2013, doi: 10.1208/s12248-013-9492-4; 2013.

SVII.4.2 Unpublished references

c02344198-01 Idarucizumab (BI 655075). Summary of Clinical Safety. 29 Jan 2015.

c02742738-02 Randomised, double-blind, placebo-controlled, two-way crossover phase Ib study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 655075 and to establish the efficacy of BI 655075 in reversal of dabigatran anticoagulant activity in volunteers. 1321.2. 18 Dec 2015.

c12723965-01 A phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous 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 (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial. Idarucizumab. 1321.3. 07 Apr 2017.

c30045812-01 Safety of potential paediatric patients treated by idarucizumab: a worldwide non-interventional chart review study. 1321.11. 14 Oct 2019.

s00018805-01 Risk Management Plan, idarucizumab, version 1.0. 27 Jan 2015.

s00018805-05 Risk Management Plan for Praxbind (idarucizumab), Version 3.1. 26 Sep 2017.

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
DLP	Data lock point
DVT	Deep vein thrombosis
EU	European Union
fc	Fragment crystallisable region (composed of 2 identical protein fragments)
LLT	Lowest Level Term
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
PD	Pharmacodynamics
PE	Pulmonary embolism
PK	Pharmacokinetics
PT	Preferred Term
RMP	Risk management plan
SMQ	Standardised MedDRA Query

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	None
Important potential risks	Hypersensitivity*
	Immunogenicity*
	Thrombotic events*
Missing information	Paediatric patients
	Pregnancy/breast-feeding
	Re-exposure to idarucizumab

* The position of the MAH is that hypersensitivity, immunogenicity, and thrombotic events do not meet the criteria for important potential risks. However, the MAH accepted them as such, following the completed EU variation (procedure EMEA/H/C/003986/II/0007).

SVIII.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There is an adverse reaction follow-up questionnaire to routinely solicit information regarding hypersensitivity and immunogenicity (important potential risks) and re-exposure to idarucizumab (missing information), see Appendix 4.

There are no other forms of routine pharmacovigilance activities for the safety concerns.

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

PART III.4 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This part is not applicable as there are no planned or ongoing post-authorisation efficacy studies imposed for idarucizumab.

PART IV.1 REFERENCES

Not applicable

ABBREVIATIONS

Not applicable

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hypersensitivity	*Routine risk communication:* SmPC section 4.4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* Idarucizumab is available as a prescription-only medicine. Idarucizumab is administered in a hospital setting only, by trained medical personnel. Idarucizumab is considered to be used by experienced emergency physicians.
Immunogenicity	*Routine risk communication:* SmPC section 5.1. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* Idarucizumab is available as a prescription-only medicine. Idarucizumab is administered in a hospital setting only, by trained medical personnel. Idarucizumab is considered to be used by experienced emergency physicians.
Thrombotic events	*Routine risk communication:* SmPC sections 4.2 and 4.4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* Idarucizumab is available as a prescription-only medicine. Idarucizumab is administered in a hospital setting only, by trained medical personnel. Idarucizumab is considered to be used by experienced emergency physicians.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Paediatric patients	*Routine risk communication:* SmPC section 4.2. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* Idarucizumab is available as a prescription-only medicine.
Pregnancy/breast-feeding	*Routine risk communication:* SmPC section 4.6. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* Idarucizumab is available as a prescription-only medicine.
Re-exposure to idarucizumab	*Routine risk communication:* None proposed *Routine risk minimisation activities recommending specific clinical measures to address the risk:* None *Other routine risk minimisation measures beyond the Product Information:* Idarucizumab is available as a prescription-only medicine.

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity	SmPC section 4.4.	Adverse reaction follow-up questionnaire (Appendix 4)
Immunogenicity	SmPC section 5.1.	Adverse reaction follow-up questionnaire (Appendix 4)
Thrombotic events	SmPC sections 4.2 and 4.4.	None
Paediatric patients	SmPC section 4.2.	None
Pregnancy/breast-feeding	SmPC section 4.6.	None
Re-exposure to idarucizumab	None proposed	Adverse reaction follow-up questionnaire (Appendix 4)

PART V.4 REFERENCES

Not applicable

ABBREVIATIONS

SmPC	Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR PRAXBIND (IDARUCIZUMAB)

This is a summary of the risk management plan (RMP) for Praxbind. The RMP details important risks of Praxbind, how these risks can be minimised, and how more information will be obtained about Praxbind's risks and uncertainties (missing information).

Praxbind's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Praxbind should be used.

This summary of the RMP for Praxbind should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Praxbind's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

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

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

It contains idarucizumab as the active substance and it is given by two times 2.5 g/50 mL solution for injection/infusion (intravenously).

Further information about the evaluation of Praxbind's benefits can be found in Praxbind's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Praxbind, together with measures to minimise such risks and the proposed studies for learning more about Praxbind's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Praxbind is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Praxbind are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Praxbind. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	Hypersensitivity
	Immunogenicity
	Thrombotic events
Missing information	Paediatric patients
	Pregnancy/breast-feeding
	Re-exposure to idarucizumab

II.B Summary of important risks

Hypersensitivity (important potential risk)	
Evidence for linking the risk to the medicine	There is a general risk from proteins to cause hypersensitivity reactions. Idarucizumab is a humanised antibody (protein) and does not contain the section of the protein that in general can cause hypersensitivity reactions. Thus, the risk for hypersensitivity reactions in patients treated with Praxbind is rather low. Based on the results from the Phase III trial 1321.3 and in line with data from spontaneous reporting, there were no facts or evidence that events of hypersensitivity were related to idarucizumab treatment. Therefore, there is no need for risk minimisation measures for the important potential risk 'hypersensitivity'.

II.B Summary of important risks (cont'd)

Hypersensitivity (important potential risk) (cont'd)	
Evidence for linking the risk to the medicine (cont'd)	However, following the completed EU variation (procedure EMEA/H/C/ 003986/II/0007) to include hypersensitivity as important potential risk in the RMP, the MAH updated the EU RMP to version 3.1 (dated 26 Sep 2017) and retains this safety concern as an important potential risk also in this updated RMP version 4.0. The position of the MAH remains that hypersensitivity does not meet the criteria of an important potential risk.
Risk factors and risk groups	Risk groups or risk factors are unknown.
Risk minimisation measures	SmPC section 4.4.
Additional pharmacovigilance activities	None
Immunogenicity (important potential risk)	
Evidence for linking the risk to the medicine	Based on the results from the Phase III trial 1321.3 and in line with data from spontaneous reporting, there were no facts or evidence that events of immunogenicity (immunogenicity describes the ability of a substance to trigger a reaction of the body's immune system) were related to idarucizumab treatment. Therefore, there is no need for risk minimisation measures for the important potential risk 'immunogenicity'. However, following the completed EU variation (procedure EMEA/H/C/ 003986/II/0007) to include immunogenicity as important potential risk in the RMP, the MAH updated the EU RMP to version 3.1 (dated 26 Sep 2017) and retains this safety concern as an important potential risk also in this updated RMP version 4.0. The position of the MAH remains that immunogenicity does not meet the criteria of an important potential risk.
Risk factors and risk groups	Risk groups or risk factors are unknown.
Risk minimisation measures	SmPC section 5.1.
Additional pharmacovigilance activities	None
Thrombotic events (important potential risk)	
Evidence for linking the risk to the medicine	Based on the results from the Phase III trial 1321.3 and in line with data from spontaneous reporting, there were no facts or evidence that thrombotic events were related to idarucizumab treatment. Therefore, there is no need for risk minimisation measures for the important potential risk 'thrombotic events'. However, following the completed EU variation (procedure EMEA/H/C/003986/II/0007) to include thrombotic events as important potential risk in the RMP, the MAH updated the EU RMP to version 3.1 (dated 26 Sep 2017) and retains this safety concern as an important potential risk also in this updated RMP version 4.0. The position of the MAH remains that thrombotic events do not meet the criteria of an important potential risk.

II.B Summary of important risks (cont'd)

Thrombotic events (important potential risk) (cont'd)	
Risk factors and risk groups	A risk group/factor is the generation of anti-dabigatran antibodies, potentially leading to a decrease of anticoagulant effect of dabigatran after its re-initiation. Idarucizumab specifically reverses the anticoagulant effect of dabigatran. Idarucizumab does not have impact on any factor of the coagulation cascade; therefore, without re-initiation of sufficient anticoagulant treatment, patients are at the genuine risk for thrombotic events associated with their underlying conditions such as comorbidities and other thrombotic risk factors, which had constituted the treatment indication for the initial therapy with dabigatran etexilate.
Risk minimisation measures	SmPC sections 4.2 and 4.4.
Additional pharmacovigilance activities	None
Paediatric patients (missing information)	
Risk minimisation measures	SmPC section 4.2.
Additional pharmacovigilance activities	None
Pregnancy/breast-feeding (missing information)	
Risk minimisation measures	SmPC section 4.6.
Additional pharmacovigilance activities	None
Re-exposure to idarucizumab (missing information)	
Risk minimisation measures	None proposed
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Praxbind.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Praxbind.

ABBREVIATIONS

EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
MAH	Marketing authorisation holder
PSUR	Periodic safety update report
RMP	Risk management plan
SmPC	Summary of product characteristics