

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761025Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 15, 2015
From	Kathy M. Robie-Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 761025
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	February 19, 2015
PDUFA Goal Date	October 19, 2015
Proprietary Name / Established (USAN) names	PRAXBIND/ idarucizumab
Dosage forms / Strength	Injection for intravenous use/ 2.5 g/50 mL (one dose equals 2 vials, 5 g)
Proposed Indication(s)	for use in patients treated with Pradaxa when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding
Recommended:	Accelerated approval: for use in patients treated with Pradaxa when reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding

1. Introduction

Idarucizumab is a humanized antibody fragment (Fab) designed to bind to dabigatran and reverse its anticoagulant effect in adults. The Fab molecule binds to dabigatran with a higher affinity than dabigatran binds to thrombin. The sponsor has conducted a development program directed toward demonstrating pharmacologic reversal of the anticoagulant effect of dabigatran as measured by various pharmacodynamic measures of coagulation. Controlled clinical studies using clinical endpoints, such as cessation of bleeding or decrease in bleeding-associated mortality, were deemed not feasible. To support the application the sponsor has submitted three pharmacokinetic/pharmacodynamic studies conducted in volunteers and interim results of an ongoing single-arm trial in patients.

The recommended dose of idarucizumab is 5.0 g, provided as two separate 50 mL vials each containing 2.5 g idarucizumab. The complete dose of 5 g is administered intravenously, as two consecutive infusions (b) (4) or as a bolus injection. The safety and effectiveness of repeat treatment with idarucizumab have not been established.

2. Background

Chemically, idarucizumab (BI 655075) is a humanized antigen-binding fragment (Fab) designed to bind to dabigatran. Idarucizumab was generated from a mouse monoclonal antibody targeting dabigatran, humanized and reduced to a Fab fragment. It is manufactured from Chinese Hamster Ovary (CHO) cells, using standard mammalian cell culture and protein purification techniques. Purification included (b) (4)

(b) (4) The final drug product is a solution for injection filled (b) (4) into sterile glass vials containing 50 ml, with a concentration of 50 mg/mL. Idarucizumab is being proposed as a reversal agent for dabigatran.

Dabigatran etexilate (Pradaxa) is the oral prodrug of dabigatran. Pradaxa is rapidly converted to dabigatran following administration. Pradaxa (NDA 22512; Boehringer Ingelheim) was first approved October 19, 2010 and is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF), for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. As for all anticoagulants, a major adverse reaction associated with dabigatran is increased risk of bleeding. The half-life of dabigatran in healthy subjects is 12 to 17 hours. Currently there is no reversal agent for dabigatran. The Pradaxa label recommends, "In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of

bleeding.” Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited....” The label also comments that activated prothrombin complex concentrates, or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran.

3. CMC

The Quality Review (completed 10/14/2015) of the application was conducted by the review team as listed in the following table from the review. The review is presented as an Integrated Review document.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
OBP- Drug Substance	Tura C. Camilli	Division of Biotechnology Review and Research I
OBP- Assay validation and Immunogenicity	Lixin Xu	Division of Biotechnology Review and Research IV
OBP- Drug Product	Frederick Mills	Division of Biotechnology Review and Research IV
Microbiology- Drug Substance	Reyes Candau-Chacon	Division of Microbiology Assessment
Microbiology- Drug Product	Candace Gomez-Broughton	Division of Microbiology Assessment
Facilities- Drug Substance	Wayne Seifert	Division of Inspectional Assessment
Facilities- Drug Product	Don Obenhuber	Division of Inspectional Assessment
Facilities- Team Lead	Steven Fong	Division of Inspectional Assessment
Microbiology- Team Lead	Patricia Hughes	Division of Microbiology Assessment
Business Regulatory Process Manager	Melinda Bauerlein	OPRO
Application Technical Lead	Chana Fuchs	Division of Biotechnology Review and Research IV

The Integrated Review states the following conclusions and recommendations:

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA STN 761025 for Praxbind (idarucizumab) manufactured by Boehringer Ingelheim Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Praxbind (idarucizumab) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

1. Benefit/Risk Considerations:

Praxbind is proposed to be used in patients treated with dabigatran, when rapid reversal of the anticoagulant effects of dabigatran are necessary in the case of emergency surgery or urgent procedures and/or for life threatening or uncontrolled bleeding. Therefore, Praxbind may address currently unmet medical needs. Based on assessment of the manufacturing process and controls, and GMP compliance of the manufacturing facilities, the drug substance and drug product manufacturing processes are well controlled and should consistently deliver DS of desired quality.

**B. Recommendation on Phase 4 (Post-Marketing)
Commitments, Agreements, and/or Risk Management Steps, if
Approvable**

None

The review indicated that Praxbind will be available at a strength of 50 mg/mL. It will be packaged in a pack of 2 single use vials each containing 2.5g/50 mL idarucizumab. Each 2-pack is designed to deliver the full dose of 5g of idarucizumab. Excipients include Sodium acetate trihydrate, sorbitol, polysorbate 20, glacial acetic acid. The drug product is preservative free. For the labeling the review recommended that the label should specify: store in a refrigerator at 2-8°C; do not freeze; do not shake; protect from light. The review stated that stability studies support a dating period of 30 months when stored at 2-8°C and in the dark.

Review findings for the various parts of the chemistry, manufacturing and controls (CMC) information in the application are briefly summarized below. Findings of the reviews of the microbiology assessment for the application are discussed in Section 6, **Clinical Microbiology**, of this review.

Drug Substance Quality Review: OBP (by Camilli, Xu, Fuchs, 7/21/2015):

The review of the drug substance (DS) included and discussed: description and properties of the DS; DS manufacture (including process, materials and controls); filling, storing and transport; source, history and generation of the cell substrate; cell banking system, characterization and testing; controls of critical steps and intermediates; manufacturing process development; comparability assessment (for the non-clinical to clinical trial material and for clinical trial material to commercial material); characterization of the DS during development and final (included Physicochemical Characterization, Biological Characterization and Forced Degradation Pathways; details about impurities and their removal); control of DS specifications and justifications; stability information. During the review clarification was needed regarding a number of aspects of the information submitted and Information Requests were sent and sponsor responses received and these are discussed in the review.

The review describes the drug substance as follows:

3.2.S.1.2 Structure

Idarucizumab is a humanized murine Fab fragment produced in CHO cells that binds to the thrombin inhibitor dabigatran and in doing so, inhibits the anticoagulatory effect of dabigatran. Idarucizumab consists of a light chain (LC, amino acids 1-219) and a heavy chain fragment (HC, amino acids 1-225) covalently linked together by one disulfide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain. (b) (4)



Molecular Formula: C₂₁₃₁H₃₂₉₉N₅₅₅O₆₇₁S₁₁.

Molecular Weight/ Molecular Mass: Based on the amino acid sequence, the molecular mass of Idarucizumab is 47766 Da. (b) (4)

The review indicated the drug substance (DS) is manufactured in (b) (4)
Biberach, Germany (b) (4)

Regarding the drug substance the review concludes and recommends, “The Office of Biotechnology Products has reviewed the drug substance section, and has found that the data submitted in this section are adequate to support the conclusion that manufacturing of idarucizumab formulated drug substance is well controlled and leads to a drug substance that is pure and potent. Therefore, approval of BLA 761025 for idarucizumab drug substance is recommended.”

Drug Product Quality Review: OBP (by Mills, Xu, Fuchs):

This review assessed the information for the drug product (DP) critical quality attributes (CQA) submitted to support the quality target product profile (QTTP) for Praxbind. The review discussed the description and composition of the DP, components of the DP, manufacture of the DP, control of excipients, control strategy for the drug product,

(specifications, analytical procedures, validation of analytical procedures, batch analyses, characterization of impurities, justification of specifications), assessment of the container closure system, evaluation of stability, stress stability (freeze-thaw, photostability, accelerated (25°C) and long-term stability data (2-8°C)) and post-approval stability commitment.

The Review described and evaluated the immunogenicity assays for anti-drug antibodies (ADA), including assay to detect presence of neutralizing antibodies, and validation of the methods. ADA in human plasma containing K₃EDTA (as an anticoagulant) is detected by an electrochemiluminescence (ECL)-based method. A modified thrombin time (mTT) assay was developed to detect neutralizing anti-dabigatran antibodies in human plasma. The Review describes that a test item (b) (4) (b) (4)

was used as a surrogate for idarucizumab and, “Depending on the antibody concentration thrombin clotting time decreased with increasing antibody concentration in a sigmoid curve shape thus demonstrating concentration dependent reversal of the Dabigatran induced prolongation of clotting times.” Regarding the immunogenicity tests the Reviewer commented:

- 1. The results obtained indicate that the modified diluted thrombin time method is suitable for intended use to detect neutralizing anti-dabigatran antibodies in human citrated plasma after cessation of dabigatran etexilate administration and washout of residual dabigatran in plasma.*
- 2. In addition, the risk of developing any anti-dabigatran antibodies to have any potential effect on idarucizumab drug safety and efficacy are relatively low:*
 - Dabigatran is a small molecule and idarucizumab usually only used for an emergency situation. The chance to develop such anti-drug antibody is low even there is a potential cross-link.*
 - The dosage of idarucizumab (which is anti-dabigatran antibody itself) used is considerably high. If there are any anti dabigatran antibodies exist, they would be shadowed by idarucizumab during the period of idarucizumab on board.*

Drug Substance and Drug Product Facilities Review: DIA (by Obenhuber, Seifert, Fong, signed 10/8/2015):

The facilities inspection concludes, “Adequate descriptions were provided for the facilities and equipment proposed for Idarucizumab DS and DP manufacture at BIP. All proposed manufacturing and testing sites are in a state of compliance. The BLA is recommended for approval from a facilities assessment standpoint.” The Review provides the following summary and recommendation:

Microbiology:

Drug Substance:

Primary Clinical Microbiology review of the drug substance part of the application from a microbial control and microbiology product quality perspective was conducted by M.D. (Reyes) Candau-Chacon, Ph.D., Office of Pharmaceutical Quality (OPQ)/Office of Process and Facilities (OPF)/Division of Microbiology Assessment (DMA) (reviews signed 7/19/2015). The review included evaluation of the BLA submission and sponsor responses to some

information requests. The review concluded a finding of ‘SATISFACTORY’ for the following:

- **Drug substance --- general information**
- **Description of the Manufacturing Process and Process Controls --- Batches and Scale Definition**
- **Cell culture steps and process controls**
- [REDACTED] (b) (4)
- **Bacterial Endotoxin test**
- **Transport**
- **Control of Drug Substance – Specifications**
- **Control of Drug Substance – Analytical Procedures**
- **Validation of Analytical Procedures**
- **Batch Analyses**
- **Justification of Specification**
- **Container Closure System**

No conclusion was provided for **Downstream Manufacturing Process and Process Controls**.

The review commented that an information request seeking clarification of “if [REDACTED] (b) (4)

[REDACTED] .” The review indicated the response will be reviewed as an addendum to the drug substance (DS) microbial quality portion of the application.

Regarding **Control of Critical Steps and Intermediates** the review indicated that the sponsor was to provide two additional runs to qualify the [REDACTED] (b) (4) and that the information would be reviewed in an addendum to the DS microbial quality portion of the application.

Regarding **Process Validation and/or Evaluation** the review indicated that the sponsor agrees to conduct a study to validate the maximum hold times of [REDACTED] (b) (4).

[REDACTED]. The information would be reviewed in an addendum to the drug substance microbial quality portion of the application. The review found acceptable that the sponsor indicates that [REDACTED] (b) (4)

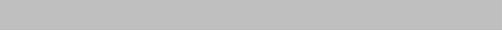
[REDACTED] will be conducted under a QA approved protocol and will include pre-established endotoxin and bioburden specifications. Regarding validation of [REDACTED] (b) (4)

[REDACTED] the review commented to the sponsor, “It is noted that due to your curren [REDACTED] (b) (4)

[REDACTED] and stated the response will be reviewed in an addendum to the DS microbial quality portion of the application.

Regarding **Stability** the review noted that no microbial quality monitoring is conducted during stability but commented that, commented that, “Microbial quality results of stability samples are not necessarily representative of microbial quality of drug substance [REDACTED] (b) (4). BDS stability is not required from a microbial quality point of view and is deferred to OBP”.

Review of microbial issues for the following aspects of drug substance manufacture was deferred to OBP:

- Control of Materials
-  (b) (4)
- 
- 
- Manufacturing Process Development
- Characterization

The review indicated that the following will be assessed during the prelicense inspection of the relevant facilities:



Although the review indicated that no approvability issues had been identified thus far, the review had the following summary recommendations:

FDA Information Request for STN 761025/0 Microbial Quality – Drug Substance
(The responses to this information request will be included as an addendum to the drug substance microbial quality portion of the BLA.)

1. Please clarify if [redacted] (b) (4)
[redacted] (b) (4)
2. Indicate when the [redacted] (b) (4) qualification report using samples from two additional batches will be submitted to the Agency
3. Submit endotoxin limits of [redacted] (b) (4) purification steps
4. Indicate when the study report for the maximum hold times of [redacted] (b) (4) [redacted] (b) (4) from microbiology perspective will be submitted to the Agency.
5. It is noted that due to your current [redacted] (b) (4)
[redacted] (b) (4)

Study reports for the qualification of [redacted] (b) (4) method and hold time validation can be submitted in the next Annual Report.

A subsequent Addendum to the Microbiology Review for the drug substance M.D. (Reyes) Candau-Chacon, PhD. (signed 8/27/2015) reviewed the sponsor's responses submitted to address the above five listed microbiology quality issues. The responses were found to be satisfactory. Notably:

- the review found it acceptable for report of the [redacted] (b) (4) qualification report using samples from two additional batches and the maximum hold validation report to be submitted in the next Annual Report
- The following table of endotoxin limits was found acceptable:

Process step / [redacted] (b) (4)	Bacterial Endotoxin process limit [EU/mL]
[redacted] (b) (4)	[redacted] (b) (4)

[redacted] (b) (4)

- The review found adequate the sponsor's proposal that the acceptance criteria for the [redacted] (b) (4)
[redacted] (b) (4)

Drug Product:

The drug product section of the application was reviewed from a microbiology perspective by C.Y. Gomez-Broughton, PhD (review signed 8/17/2015). The review found the drug product section of the application acceptable and recommended for approval from a microbial control and microbiology product quality perspective. The review indicated, “No approvability issues have been identified and the review of the pending responses to information requests will be included as an addendum to this review.” The following list of items was included in the review for communication as an Information Request:

FDA Information Request for STN 761025/0 Microbial Quality- Drug Product

P.3.3 Description of Manufacturing Process and Process Controls

Table 4 “Idarucizumab (b) (4) appears to summarize (b) (4) (b) (4) Please provide a description of the (b) (4) for the drug product manufacturing process.

P.3.4 Control of Critical Steps and Intermediates

Please amend this BLA section to include descriptions of the analytical methods used to measure (b) (4) bioburden and endotoxin.

P.3.5 Process Validation and/or Evaluation

1. Provide the filling duration for each validation run. Specifically, the duration from the (b) (4). Include definitions of the start and end time points.
2. Please submit the study reports for the (b) (4) studies completed during the initial qualification studies for (b) (4). Please include the source of the endotoxin used in the study.
3. With regard to media fill, provide the dates for the current media fill data submitted in the BLA (Batches 301033, 305591, 401000, and 406043).
4. Define the start and end time for the fill durations used during media fills.
5. Provide actions taken in the event of a media fill failure.
6. With regard to the transport validation studies, please describe the monitoring points at which temperature data was collected.
7. Provide a description and/or a diagram showing the location of the (b) (4) (b) (4)
8. Provide acceptance criteria for the transport validation studies.

FDA Information Request for STN 761025/0 Microbial Quality- Drug Product

P.3.3 Description of Manufacturing Process and Process Controls

We acknowledged your protocols for validation of (b) (4) that you have provided in your June 26, 2015 responses to the FDA. We also note that there is an (b) (4) (page 259 of your response).

Indicate if (b) (4) in the drug product manufacturing process.

Any (b) (4) steps in the drug product manufacturing process should be clearly identified in section 3.2.P.3.3, including descriptions of the conditions under which (b) (4) would occur, (b) (4) etc.

Adequate justification for these control parameters and timelines should be provided. Additionally, you should also identify in the BLA that successful results of the (b) (4) validation protocols will be submitted in an annual report.

P.3.5 Process Validation and/or Evaluation

1. Submit the (b) (4) microbial retention study report completed by (b) (4). The report should include controls, acceptance criteria, incubation conditions (b) (4) and growth promotion ability of growth media.
2. Submit the validation report for the (b) (4) integrity test. Be sure to include the following information:
 - a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)

The Integrated Review gives the following summary for CMC:

SUMMARY

The subject BLA proposes manufacture of Idarucizumab Drug Substance (DS) and Drug Product (DP) at Boehringer-Ingelheim Pharma GmbH & Co., Biberach an der Riss, Germany (BIP, FEI 307748866). BIP will also conduct Master and working cell bank storage, and DS and DP IPC testing. Additional cell banking, testing, and packaging operations will be conducted at BIP, Boehringer-Ingelheim RCV GmbH & Co. KG (3003433722), (b) (4) and (b) (4) and Boehringer Ingelheim Roxane (FEI 1510690).

Idarucizumab is a humanized murine Fab fragment directed against the thrombin inhibitor dabigatran. All listed DS manufacturing; DP manufacturing, testing and packaging facilities are acceptable. The facility descriptions submitted for this BLA have been reviewed and found to be adequate to support the manufacturer of Idarucizumab DS and DP.

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology Review of this application was conducted by E. Place, Ph.D, (See review signed in DARRTS 7/20/2015). Secondary Pharmacology/Toxicology Review was conducted by CM Sheth, Ph.D. (signed 7/28/2015). The reviews describe that safety pharmacology, pharmacokinetic and general pharmacology studies of idarucizumab were done in animals as well as in vitro studies to characterize the binding and activity of idarucizumab. Regarding in vitro studies, Dr. Place's review states:

Idarucizumab binds dabigatran with higher affinity than thrombin (~300 times higher) and thrombin substrates in vitro. Results from in vitro studies show that idarucizumab forms a stable complex with dabigatran (with 50% of bound complex remaining after 260 hours). Idarucizumab also binds dabigatran metabolites. In vitro data showed that idarucizumab reverses the anticoagulant effect of dabigatran, in part by increasing fibrin coverage and increasing fibrin masses around damaged subendothelium. Three animal models of activity were submitted in support of the application: a mouse intracranial hemorrhage model; a rat tail cut bleeding model, and a pig blunt liver trauma model. All 3 animal pharmacology models showed the effectiveness of the neutralization activity of idarucizumab, and its ability to significantly reduce anticoagulation and blood loss. Based on the pharmacology data submitted in the BLA, the Established Pharmacological Class (EPC) of "reversal agent for dabigatran" was determined to be both clinically meaningful and scientifically valid for idarucizumab.

Results of pharmacokinetic studies were described as follows:

In the pharmacokinetic studies in both rats and monkeys, there was a rapid increase in dabigatran plasma concentration following dosing with idarucizumab suggesting redistribution of dabigatran from the tissue to the plasma. Based on the data collected in general toxicology studies, there were no gender differences in exposure, and increased in C_{max} and AUC values were approximately dose proportional. Idarucizumab was rapidly eliminated in the blood following intravenous dosing and exhibited biphasic plasma concentration-time profiles; initial phase half-lives were approximately 0.25 hrs. (both species) and terminal phase half-lives were approximately 6 hrs in the rat and 5.5 hrs. in the monkey.

The primary review states that safety pharmacology studies showed no adverse respiratory effects and indicated that independent cardiovascular safety pharmacology studies were not done but electrocardiographic measurements in the monkey repeat dose toxicology studies were unremarkable up to 500 mg/kg.

The primary review summarizes the toxicology studies as follows:

The general toxicology studies were conducted in the rat and monkey via I.V., which is the intended route of administration for idarucizumab. The rat studies were performed using only idarucizumab; the monkey studies were performed in the presence and absence of orally administered dabigatran. The 4 week repeat dose toxicity study in rat and 2 week repeat dose toxicity study in the monkey are reviewed. All appropriate studies were conducted in compliance with Good Laboratory Practice (GLP) regulations. There were no major target organs in rat or monkey.

The following types of toxicological assessments for idarucizumab were not deemed essential for marketing due to the specific nature of its intended use, which is as a single administration only when needed to rapidly reverse the anticoagulant effects of dabigatran: in vitro and in vivo genotoxicity, carcinogenicity, reproductive and developmental toxicity, fertility, embryo-fetal development; and pre- and postnatal development toxicity testing.

The primary Pharmacology/Toxicology review concludes that “From the Pharmacology/Toxicology perspective “idarucizumab” may be approved for the proposed indications.” The review stated that, “Based on the pharmacology data submitted in the BLA, the Established Pharmacological Class (EPC) of “reversal agent for dabigatran” was determined to be both clinically meaningful and scientifically valid for idarucizumab.” There were no additional non-clinical recommendations. The secondary Pharmacology/Toxicology Review concurred with the primary review that from a nonclinical perspective, idarucizumab “may be approved and that no additional nonclinical studies are needed to support approval of PRAXBIND in patients with treated with Pradaxa® when rapid reversal of the anticoagulant effects of dabigatran is required.”

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology Review of this application was conducted by M.D. Sahre, PhD and D. Rekid, PhD. (See review signed in DARRTS 8/10/2015). Additional Pharmacometrics Review was completed by D. Rekid, PhD (signed 9/15/2015). The primary Clinical Pharmacology Review summarizes the following salient findings of the review:

Idarucizumab pharmacokinetics

- Idarucizumab disposition is dominated by the rapid initial distribution half-life of around 45 min. Idarucizumab declines to less than 20% of its peak concentrations 2 h after administration.
- Idarucizumab displayed dose-linear kinetics for doses ranging from 20 mg to 8 g.
- Idarucizumab, as an antibody fragment, is likely metabolized by proteases in vivo, and excreted renally. Renal excretion of idarucizumab ranged from 8 to 40% in the range from 1 to 8 g, pooled over available studies. This may be due to saturable catabolism or tubular reabsorption in the kidney.
- Age (20 to 76 years), sex, and race (Asians vs. Whites) did not influence idarucizumab disposition in a clinically relevant manner.
- When administered to patients with mild and moderate renal impairment, idarucizumab exposure (AUC) increased by 40% and 80%, respectively. Given that dabigatran exposure also increases with renal impairment, no dose adjustment is necessary for mild or moderate renal impairment as the effects of exposure increase for both idarucizumab and dabigatran goes in the same direction.
- Idarucizumab does not distribute extensively to peripheral tissues. Its volume of distribution is estimated to be 5 – 8 L, suggesting that idarucizumab is mainly present in interstitial fluid.

Idarucizumab Pharmacodynamics

- Idarucizumab has no intrinsic pro-thrombotic effect as shown by its lack of effect on coagulation markers or on the endogenous thrombin potential.
- Administration of 5 g of idarucizumab at steady-state exposures of dabigatran causes an immediate decrease of unbound dabigatran concentrations in most patients.
- Coagulation markers ECT, aPTT, TT, and dTT follow the pharmacokinetics of unbound dabigatran closely, thereby leading to immediate reversal of dabigatran mediated anticoagulant activity in most of the patients.
- Dabigatran redistribution peaks between 2.3- 18.4 ng/mL were observed in all subjects (n=26) that received the 5 g dose in study 1321.2. The peaks occurred around ~24 hours following idarucizumab administration. One subject had a distribution peak of 46 ng/mL.

- Redistribution resulting in dabigatran exposures exceeding 50 ng/mL, a detectability threshold that represents dabigatran-induced anticoagulant activity, is likely to occur in subjects with pre-dose unbound sum dabigatran concentrations above 190 ng/mL. Based on data from the RE-LY, redistribution of this magnitude may occur in at least 10% of patients receiving dabigatran 150 mg BID.
- For patients with very high initial dabigatran concentrations (>600 ng/mL, unbound sum), 5 g of idarucizumab is unlikely to suppress the effects of dabigatran. Three (out of 30) patients were observed to have dabigatran concentrations at these high levels in the on-going open label Phase 3 study. Anticoagulation due to dabigatran was not completely reversed in these subjects.
- Repeat administration two months after initial treatment with idarucizumab showed similar suppression of unbound sum dabigatran exposures with a corresponding reversal of dabigatran-induced anticoagulant activity.
- Re-initiation of dabigatran treatment 24 hours after treatment with idarucizumab results in comparable unbound sum dabigatran concentrations and anticoagulant activity before and after idarucizumab treatment.

In conclusion, the Clinical Pharmacology Review determined that, “pending the inspection results for one of the analytical sites and labeling agreement, there is sufficient clinical pharmacology information provided in the NDA to support approval of idarucizumab for the rapid reversal of the anticoagulant activity of dabigatran in emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding.” Importantly, the review recommended that:

The labeling should include a warning that elevated coagulation parameters will occur in some patients (due to redistribution of dabigatran) with the proposed 5 g idarucizumab dose. If such elevations in coagulation parameters are associated with reappearance of clinically relevant bleeding, an option for re-dosing idarucizumab (5g) in those patients should be provided in the label.

There were no recommendations for Phase 4 study commitments.

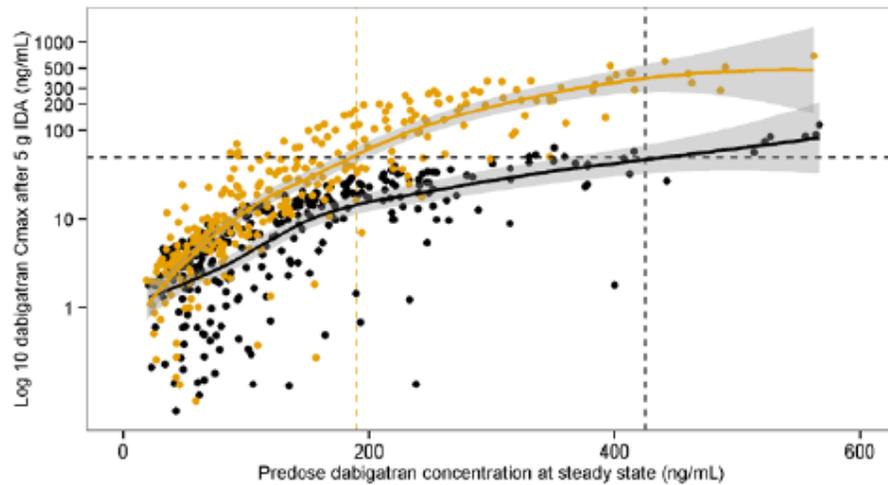
Additional Pharmacometric Review was conducted to address questions about dosing of idarucizumab with the following findings. (See Pharmacometric Review by D. Rekić, 9/15/2015).

➤ **Is the proposed idarucizumab dose (5 g) appropriate for the target population?**

The review concluded, “Yes.” The review found that the dose was adequately supported. The review found that, “dabigatran suppression in these healthy volunteer studies was achieved at concentrations that are comparable to those observed in the original dabigatran registration trials for the treatment of venous thromboembolism and the prevention of stroke in patients with atrial fibrillation.” The review states that, “The proposed dose of 5 g idarucizumab appears to be sufficient to suppress dabigatran concentrations in plasma and to reverse the pharmacological effect of dabigatran on blood coagulation parameters in most subjects.” Age was not found to be a determinant of dabigatran suppression. Doses lower than 4 g were found to be inadequate to suppress dabigatran in most subjects.

- **What is the effect of idarucizumab administration on dabigatran exposure from the ongoing Phase 3 trial?** In examining the available results in the ongoing open-label use of idarucizumab in patients the review found that, “The recommended idarucizumab dose of 5 g is adequate to suppress dabigatran exposure in most patients. However, at high dabigatran concentrations (pre-idarucizumab administration), dabigatran levels may not be adequately suppressed. In addition, dabigatran concentration may return to levels above the limit of quantification and result in detectable anticoagulation due to redistribution of dabigatran from peripheral tissue.” The review states that the 5 g idarucizumab dose was inadequate to suppress dabigatran in a patient with plasma concentrations close to 3000 ng/mL and describes that, “The 5 g idarucizumab dose was able to initially suppress dabigatran in the patient with plasma concentrations close to 1500 ng/mL. However, due to redistribution from peripheral tissues, dabigatran concentrations returned close to 1000 ng/mL 4 h after idarucizumab administration and continued to increase up to 1500 ng/mL at 12 h after idarucizumab dose. No observations are available after 12 h in this subject.”
- **Is there a need to adjust the idarucizumab dose in patients with renal impairment?** The review concluded, “No.” The review commented that the clinical studies did not show moderate or mild renal impairment to be a determinant of dabigatran suppression 12 subjects at the proposed 5 g idarucizumab dose. The review conducted further clinical trial simulations and inferred the following:
 - **Renal impairment (severe, moderate, or mild) is not a determinant of dabigatran suppression because both dabigatran and idarucizumab elimination is dependent on renal function. Both dabigatran and idarucizumab exposure will increase with decreasing renal function.**
- **Is there a subpopulation where the proposed dosing regimen may result in inadequate dabigatran suppression?** The review concluded, “Yes.” Simulations were conducted for steady-state trough concentrations versus the maximum re-distribution dabigatran concentration. The review states, “Steady state unbound total dabigatran trough concentrations are a predictor of inadequate dabigatran suppression. Steady-state pre-dose unbound total dabigatran concentrations >190 ng/mL are likely to result in therapeutic dabigatran concentrations (>50 ng/mL) 5 to 12 h after idarucizumab infusion due to redistribution from peripheral tissues if idarucizumab is administered 2 h after the last dabigatran dose. This is considered a worst-case scenario (**Figure 7**). Idarucizumab administration 12 h after the last dabigatran dose is considered a best-case scenario; give (*sic*) that dabigatran is administered BID. Under the best-case scenario: pre-dose unbound total dabigatran concentrations >420 ng/mL are likely to result in therapeutic dabigatran concentrations (>50 ng/mL) 5 to 12 h after idarucizumab infusion due to redistribution from peripheral tissues (**Figure 7**). These finding are relevant to pre-dose concentration of dabigatran that are < 600 ng/mL. At concentrations higher than 600 ng/mL, 5 g of idarucizumab may be inadequate to suppress dabigatran or result in a dabigatran redistribution peak that occurs earlier (**Figure 4**, observed data from ongoing Phase 3 trial). This relationship does not hold if the reason for the high dabigatran exposure is renal impairment...”

Figure 7: Simulated Steady-State Dabigatran Trough Concentrations Versus The Maximum Re-Distribution Dabigatran Concentration



Note: Pre-dose steady state unbound total dabigatran trough concentrations (x axis) are plotted versus the maximum unbound total dabigatran concentration after idarucizumab infusion.

The worst-case scenario (yellow) assumes idarucizumab administration 2 h after the last dabigatran dose (at approximate C_{max}). The best-case scenario (black) assumes idarucizumab administration 12 h after the last dabigatran dose.

The circles represent individual observations. The lines are non-parametric smoothers (loess) used for illustration purposes. The shaded area is the 95% CI around the loess line. The horizontal dashed line represents the 50 ng/mL cut off. The yellow vertical dashed line denotes the 190 ng/mL cut off for the worst-case scenario, while the black vertical dashed line denotes the 420 ng/mL cut off for the best-case scenario.

Source: Simulated based on models run2113.mod and run2115.mod

- **What is the clinical relevance of dabigatran redistribution following idarucizumab administration and what options are available to address it?** The review finds redistribution of dabigatran following idarucizumab administration may be clinically relevant. The review provides the following analysis and recommendations:

The proposed indication for idarucizumab is for patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required. Current guidelines for patients undergoing surgery recommend discontinuation of dabigatran 24 h to 5 days before the procedure, depending on renal status and risk of bleeding². Table 2 shows the recommendations and the predicted dabigatran plasma concentrations at the shortest recommended time. Patients with a standard bleeding risk are generally recommended to have dabigatran concentrations <15 to 20 ng/mL. Based on these recommendations, the elevated dabigatran concentrations due to the redistribution from peripheral tissue may also be clinically significant.

In case of emergency surgery or uncontrolled bleeding, the option to postpone the procedure until dabigatran levels have decreased to sufficiently low levels or to measure dabigatran concentration directly may not be realistic. Instead, current clinical practice guidelines recommend monitoring aPTT to determine the presence of dabigatran³. The relationship between dabigatran and the four major coagulation markers (ECT, dTT, aPTT, and TT) is shown below in **Figure 8**. Based on the available data, it may not be possible to detect dabigatran concentrations that are in range listed in **Table 2** (5-20 ng/mL) due to variability between dabigatran concentration and the coagulation markers. On the other hand, dabigatran concentrations >50 ng/mL are associated with a high likelihood of coagulation tests exceeding the upper limit of normal (ULN). Altogether, the redistribution phenomenon was deemed highly clinically significant by this reviewer if it resulted in unbound total dabigatran concentrations >50 ng/mL because:

- An unbound total dabigatran concentration >50 ng/mL is very likely to be detectable using any of the four coagulation markers. Depending on the marker, the likelihood that a coagulation marker will be above the ULN is 97.1 to 99.7%. ULN is defined as two standard deviations above the normal (mean) estimate of that biomarker from available data.
- Concentration of unbound total dabigatran at ~50 ng/mL were observed in the Phase 3 dabigatran trial) in patients with mild renal impairment administered 150 mg b.i.d. (Figure 3). As there was efficacy in this subgroup of patients in the trial it is inferred that meaningful anticoagulation occurs at these dabigatran concentrations.

It should be noted that concentrations < 50 ng/mL might be clinically significant as well. Flexibility in labeling should be afforded physicians to determine the clinical significance of elevated coagulation markers in their patient following idarucizumab administration. For example, if the option to wait until dabigatran is naturally eliminated is not viable as may be the case with emergency surgery, or if a patient is presenting with uncontrolled bleeding, labeling should permit administration of a second dose of idarucizumab based on clinical judgment. Such an approach may be particularly useful in situations when clinical signs of bleeding persist or reoccur 12 hours after the initial idarucizumab administration and anticoagulation tests confirm that coagulation markers have not returned to baseline.

³ [Cushman, Mary, et al. "Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic Drug-Associated Bleeding Complications in Adults" February 2014](#)

Table 2: Guide to the discontinuation of dabigatran before elective surgery in patients with a standard or high risk of bleeding

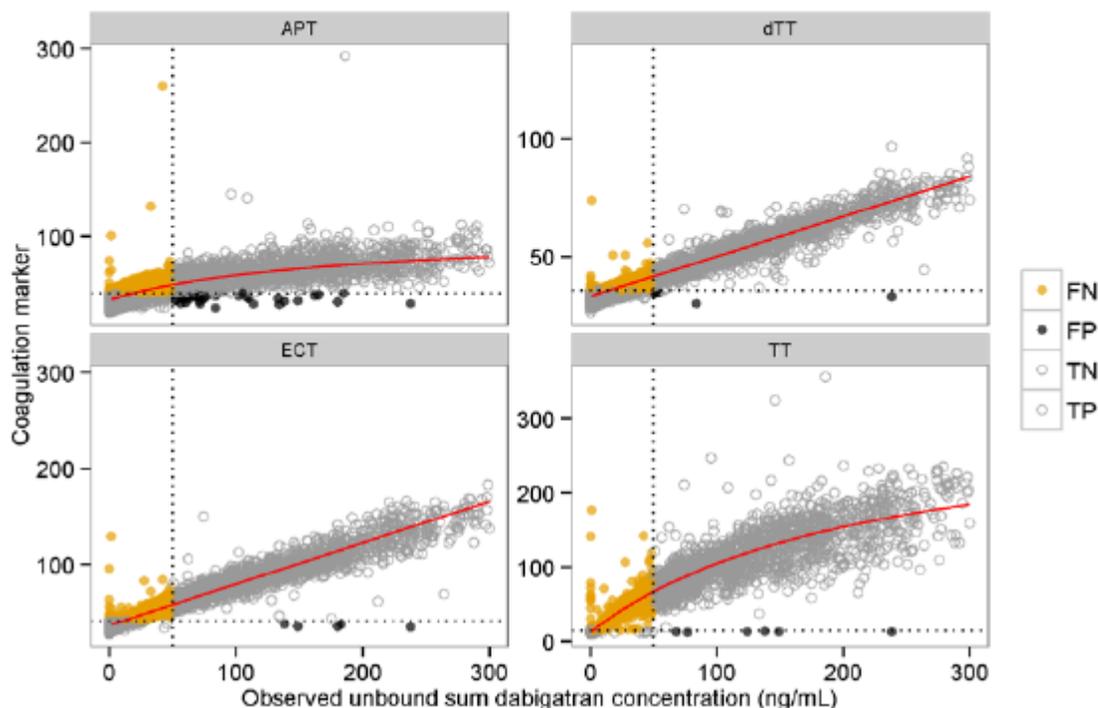
Copyright Material Withheld	Estimated median unbound total dabigatran plasma concentration after the shortest recommended time before surgery ^c	
	Standard risk of bleeding	High risk of bleeding ^b
Copyright Material Withheld	14.9 ng/mL	5.8 ng/mL
	22.9 ng/mL	9.5 ng/mL
	14.1 ng/mL	3.21 ng/mL
	10.9 ng/mL	1.84 ng/mL

^c Estimated based on simulations using applicant's population PK model (run2109.mod). CRCL clearance cut-off limits where different from those used by applicant. The cut-off values where: 90 to 210 mL/min, 60 to 90 mL/min, 30 to 60 mL/min, and 15 to 30 mL/min.

Note: Table adapted from Van Ryn, et al. 2010²

² Van Ryn, Joanne, et al. "Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity." *Thrombosis & Haemostasis* 103.6 (2010): 1116.

Figure 8: Exposure response relationship of dabigatran and aPTT, dTT, ECT, and TT



Note: Orange circles represent individual dabigatran concentration observations < 50 ng/mL that were also above the upper limit of normal (ULN) value for that coagulation marker (dotted horizontal line). These observations are considered false positive (FN).

Black circles represent individual dabigatran concentration observations > 50 ng/mL dabigatran that were also below the upper limit of normal (ULN) value for that coagulation marker. These observations are considered false negative (FP).

Gray circles represent individual dabigatran concentration observations that are on the right side of the upper limit of normal (ULN) value for that coagulation marker and the 50 ng/mL cut-off. These observations are considered to be true positive (TP) and true negative (TN).

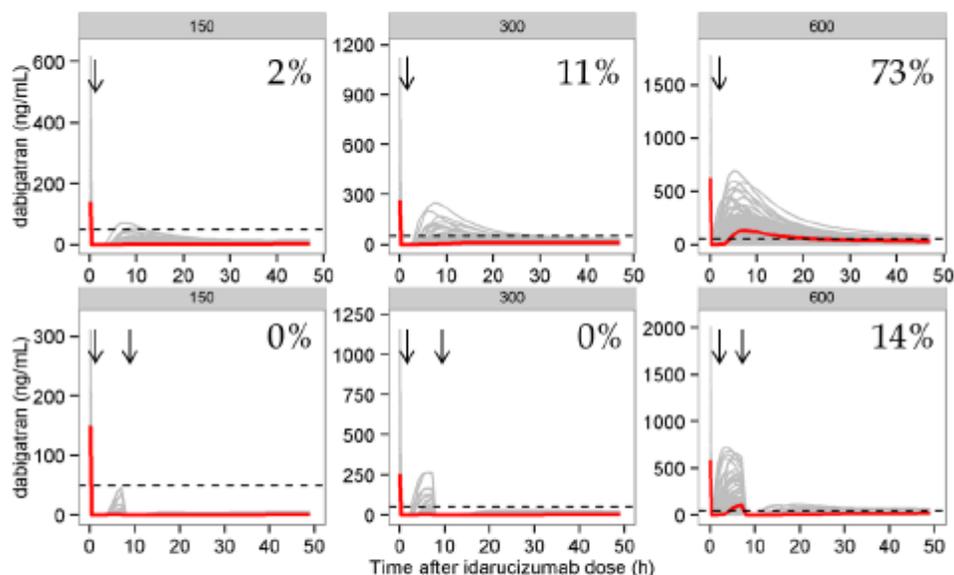
The red line represents the population exposure response relationship estimated by the applicant.

Source: Data: comb-ppbtsumngml-data-nov062014.xpt, model fit: applicants report, table 10.2.1, ULN values: c02742738, Appendix 16.1.9.3, Table 1.9

Simulations using the applicant's model illustrate the effect of either one or two doses of idarucizumab on dabigatran exposure in patients at therapeutic doses of dabigatran or two and four times the therapeutic dose of dabigatran (Figure 9).

Upper panels of Figure 9 show the effect of one dose of idarucizumab on 150, 300, 600 mg dabigatran b.i.d. The dashed horizontal line illustrate the 50 ng/mL cut-off and the percentages on each panel show the percent of subjects projected to have dabigatran concentrations above the cut-off after one idarucizumab dose. The lower panels illustrate the effect of two idarucizumab doses given 6 h apart.

Figure 9: Simulated dabigatran concentration time profile following one (upper panels) or two (lower panels) doses of idarucizumab



Note: Each panel shows the effects of idarucizumab on dabigatran following a 150, 300, or 600 mg b.i.d. dosing regimen. Individual predictions are shown as gray lines; the red line is the median. The dashed horizontal line is the 50 ng/mL cut-off. The percentage points shows the probability of observing concentration above the cut-off following one idarucizumab dose (upper panels) or two idarucizumab doses 6 h apart (lower panels). Stochastic simulations with between subject variability and residual error. Each panel consists of 100 individuals.

Source: Simulated with model run2113.mod (upper panel) and run2114.mod (lower panel)

The Pharmacometrics Review states the following recommendations:

This reviewer recommends approval provided that the Agency and the applicant can come to agreement regarding the labeling language. It is recommended that labeling include language describing that dabigatran redistribution from peripheral tissues may occur and that such redistribution can be detected using anticoagulation tests. Labeling should also permit practitioners flexibility to allow for repeat dosing of idarucizumab in cases of non-complete reversal of the effects of dabigatran (e.g., clinical symptoms of bleeding persist and anticoagulation tests indicate coagulation exceeding baseline values).

6. Clinical Microbiology

For review of microbiological aspects of the application see section 3 CMC above.

7. Clinical/Statistical- Efficacy

The primary Clinical Review of efficacy for this application was conducted by A. Dmytrijuk, MD with secondary sign-off by K. Robie Suh, MD, PhD (See Clinical Review signed in DARRTS 8/27/2015).

The Clinical Review summarizes the support for efficacy of idarucizumab for the indication: for use “in patients treated with dabigatran (Pradaxa®) when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding” as follows:

“The sponsor has provided substantial evidence to support the approval of idarucizumab from two phase 1 pharmacokinetic and pharmacodynamic studies which demonstrated that idarucizumab is able to reverse the pharmacodynamic effects of dabigatran, based on coagulation tests, in adult normal healthy volunteers at steady state. Support for this conclusion is demonstrated in two phase 1 studies (studies 1321.1 and 1321.2 described in detail below in section 4.5 Clinical Pharmacology). These were randomized, placebo controlled, double-blind, studies in which dabigatran 220mg was administered orally twice daily for 3 days with an additional 220mg dose administered on day 4 followed by single or divided intravenous idarucizumab infusions of up to 8g. These studies demonstrated that there was a dose dependent reversal of the pharmacodynamic effect of dabigatran by idarucizumab in normal healthy volunteers who received intravenous single or split doses of idarucizumab ranging from 20mg to 8g administered over up to 1 hour or two 2.5g infusions over 5 minutes up to 1 hour apart following dabigatran administration. From a clinical perspective, the reversal of the pharmacodynamic effect of dabigatran by idarucizumab was established using several different coagulation tests, e.g., dilute thrombin time (dTT), thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT). In these two studies 159 subjects were exposed to idarucizumab. Additional supportive safety and efficacy data comes from an ongoing phase 3 (study 1321.3 described in detail below (see the Review of Relevant Individual Trials Used to Support Efficacy) which has enrolled 123 adult patients who are being treated with dabigatran and require emergency surgery or procedures for other morbidities or are being treated with dabigatran and present with life-threatening or uncontrolled bleeding. Data from this interim analysis demonstrates that administration of two doses of idarucizumab 2.5 mg intravenously 15 minutes apart can rapidly reverse and sustain the reversal of the pharmacodynamic anticoagulant effect of dabigatran for at least 24 hours after the last administration of idarucizumab.”

8. Safety

The primary Clinical Review of safety for this application was conducted by A. Dmytrijuk, MD with secondary sign-off by K. Robie Suh, MD, PhD (See Clinical Review signed in DARRTS 8/27/2015).

The safety database in patients who received idarucizumab come from Study 1321.3, titled “A Phase III, Case Series Clinical Study of the Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration of 5.0 g Idarucizumab in Patients Treated with Dabigatran Etexilate Who Have Uncontrolled Bleeding or Require Emergency Surgery or Procedures, the REVERSE –AD Trial.” As described in Dr. Dmytrijuk’s Clinical Review Study 1321.3 is “an open label, multicenter, single arm, safety and efficacy trial in which the sponsor plans to enroll up to 300 adult patients. The primary objective is to demonstrate reversal of the anticoagulant effect of dabigatran in patients treated with dabigatran who have uncontrolled or life-threatening bleeding requiring urgent intervention, and in patients treated with dabigatran who require emergency surgery or other invasive procedure. The key enrollment criteria are bleeding that requires a reversal agent in the opinion of the physician, urgent requirement for surgery or an invasive procedure where adequate hemostasis is required and patients must be taking dabigatran. In this study Idarucizumab is administered at a 5g fixed dose administered as two 2.5g doses administered over 5-10minutes separated by 15 minutes or as a bolus. Biomarker endpoints are the basis for determination of efficacy in this trial. Ecarin clotting time (ECT), diluted Thrombin Time (dTT), activated Partial Thromboplastin Time (aPTT) and Thrombin Time (TT) are measured in a central laboratory.” As of April 1, 2015 (cutoff for 120-Day Safety Update) a total of 123 patients have been enrolled and treated. All have received the 5 g dose of idarucizumab with an infusion time of 5 minutes.

The Clinical Review summarizes the patient characteristics as follows:

“There were 66 patients in Group A (bleeding) and 57 patients in Group B (surgery).... Overall, the baseline demographics were similar between groups. Overall, the median age was 77 years (range 48-93), 65/123 (53%) were male and 105/123 (85%) were white. There were 49/123 (40%) of patients enrolled with moderate to severe renal insufficiency, i.e., CrCl (Cockcroft-Gault) < 50mL/min. Overall, the median time from last dabigatran exposure to the time of idarucizumab administration was 16 hours (range 1-94 hours). Nearly all patients, i.e., 117/123 (95%) were treated with dabigatran for the atrial fibrillation indication. Most patients, i.e., 80/123 (65%) were treated with dabigatran 110mg orally twice daily. In group A (serious bleeding group) there were 27/66(41%) who presented with gastrointestinal bleeding, 24/66 (36%) patients presented with intracranial bleeding, the remaining 15/66 (22%) of patients had serious bleeding in other areas such as trauma, intramuscular, retroperitoneal, intra-pericardial, intra ocular and one bleeding location was not yet identified by the sponsor. Of the 57 patients in group B (urgent surgery group) surgery that was required in ≥ 3 patients was bone fractures 13/57 (23%) of patients, gall bladder disease (cholecystitis, cholelithiasis) 7/57 (12%) of patients, joint/wound infection 4/57 (7%) of patients and acute appendicitis, small bowel obstruction, bowel perforation in 3/57 (5%) each, respectively.”

The Clinical Review reports there were 26 deaths among the 123 patients treated-- 13 in Group A (serious bleeding) and 13 in Group B (urgent surgery) and with 13 of the deaths occurring in the first 5 days from study treatment. Serious adverse events leading to death in these patients included: cardiac arrest, circulatory collapse, Brain edema (intracranial hemorrhage progression), aortic aneurysm rupture, cardiogenic shock, peritonitis and hemorrhagic anemia, shock, septic shock, sepsis and shock and gastrointestinal hemorrhage, multi-organ failure, pulmonary edema, cardiac failure acute, cerebral infarction, cardiac failure congestive, pancreatic carcinoma, pneumonia and septic shock, general health deterioration, Parkinson's disease, gastrointestinal hemorrhage, pneumonia, and malignant neoplasm progression.

Regarding Immunogenicity, the Clinical Review states:

Sampling for anti-drug antibodies (ADA) against idarucizumab in study 1321.3 was planned for pre-dose (Visit 1) and one or more post-dose samples (30±7 days and 90±7 days, Visits 5 and 6, respectively). Not all patients were sampled for the development of antidrug antibodies (ADAs). Data are available for 47/123 patients with a pre-dose sample and at least one post-dose sample. The sponsor reports that 2 patients with baseline, non-specific ADAs (patients (b) (6) and (b) (6)) had persisting ADAs at day 30 day but the binding is not at the variable site. One more patient (patient (b) (6)) had a treatment emergent ADA at day 30 of mixed specificity.

In the Clinical Review, Dr. Dmytrijuk comments: "The mortality rate observed in study 1321.3 can be expected given the serious conditions of the enrolled patients in study 1321.3. Overall, SAEs reported in study 1321.3 in ≥ 2 patients included pneumonia, deep vein thrombosis, pulmonary embolism and acute renal failure. No significant differences were observed between treatment groups in terms of SAEs reported in study 1321.3. In addition, no significant changes in clinical laboratory tests, immunogenicity, QT evaluations.

The Clinical Review comments conclude:

Overall, the benefit of idarucizumab to reverse the pharmacodynamic effect of dabigatran in patients who require emergency surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required is favorable. Significant safety risks have not been identified in this review.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

10. Pediatrics

No pediatric subjects were studied for this application. Dr. Dmytrijuk's Clinical Review (8/27/2015) states, "Dabigatran is not approved in the US for use in pediatric patients. The sponsor requests a full waiver of the requirement for pediatric studies in 21 CFR Section 314.55 (a) that each application for a new dosage form contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric sub-populations. The sponsor states that idarucizumab is not likely to be used in a substantial number of pediatric patients treated with dabigatran who require emergency

surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required. The sponsor states that necessary studies are impossible or highly impractical because the number of such patients is low.” The Clinical Review recommends that the sponsor’s request is reasonable and a full waiver of the requirement in 21 CFR Section 314.55 (a) should be granted.

CDTL Reviewer comment: Currently dabigatran is indicated only for use in adult patients and, consequently, it is anticipated that any use of idarucizumab would be very uncommon, such that pediatric studies would be impractical or impossible. Accordingly, it is reasonable that the sponsor’s request for waiver of pediatric studies of idarucizumab be granted. It should be noted, however, that should indications and target patient populations for use of dabigatran as an anticoagulant be expanded to pediatric patients, it may be appropriate to encourage studies of idarucizumab in pediatric patients at that time.

11. Other Relevant Regulatory Issues

Proprietary name review:

The proposed proprietary name, Praxbind, was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA)/Office of Medication Error Prevention and Risk Management (OMEPRM)/Office of Surveillance and Epidemiology (OSE) which found the proposed name acceptable from both a promotional and safety perspective. (See review by N. Vora, signed 1/14/2015). A Proprietary Name Conditionally Acceptable letter was sent to the applicant on 1/18/2015.

Office of Surveillance and Epidemiology Review (OSE)/Office of Pharmacovigilance and Epidemiology (OPE):

The Office of Pharmacovigilance and Epidemiology (OPE)/ Division of Epidemiology I (DEPI-1) provided comments and recommendations for a postmarketing clinical safety study for idarucizumab (See review memo by K. Gelperin, MD, 9/15/ 2015). Citing the small size of the clinical trial database, OPE comments and recommends as follows:

Although no cases of serious hypersensitivity reactions have been identified to date in patients exposed to idarucizumab, the limited clinical experience thus far is not sufficient to rule out potential issues with immunogenicity, or other serious adverse drug reactions, postmarketing. It is anticipated that FAERS data will be difficult to interpret, and there is a potential for a large number of spontaneous reports with fatal outcomes due to the high mortality expected in the indicated population. Unfortunately, claims data, and methods using Sentinel, are unlikely to provide useful safety information given current limitations of these data sources to capture parenteral infusions in hospital Emergency Department settings.

The current ongoing clinical study (1321.3) has a target enrollment of 300 patients. Based on the “rule of threes” this sample size can provide some reassurance that a serious adverse drug reaction of interest is unlikely to occur in more than 1% of patients treated with idarucizumab if no events are observed during the study.

DEPI recommends issuing a PMR for a clinical safety study (similar to Study 1321.3) to provide additional reassurance that serious adverse drug reactions, such as serious hypersensitivity reactions, do not occur commonly with idarucizumab. A target sample size of 1000 exposed patients (including the 300 patients from Study 1321.3) could provide reassurance that serious adverse drug reactions not observed during the study are unlikely to occur in more than three per thousand patients treated with idarucizumab.

DEPI also recommends the sponsor conduct an evaluation to compare mortality rates among dabigatran exposed patients who have a major hemorrhage / emergency surgery who receive idarucizumab (this trial) versus dabigatran exposed patients who have a major hemorrhage / emergency surgery and do not receive idarucizumab (from historical dabigatran trials).

Division of Risk Management (DRISK) Risk Evaluation and Mitigation Strategy (REMS) Review:

Risk Evaluation and Mitigation Strategy (REMS) Review was conducted by CL Yancey, MD (review signed 8/14/2015).

The review comments that the most important serious risks associated with idarucizumab are thrombotic events, stating:

The most important serious risks associated with use of idarucizumab are thrombotic events (of the patient's underlying disease) when dabigatran anticoagulant therapy is discontinued and idarucizumab reversal anticoagulant therapy is initiated and the potential risk of using idarucizumab in a patient with known hypersensitivity to idarucizumab or to any of the excipients. At this time, immunogenicity data suggests that idarucizumab has low immunogenic potential (i. e., low incidence of treatment-emergent anti-idarucizumab antibodies and low titers). The most common adverse reaction reported with use of idarucizumab is headache (12 of 224, 25% and placebo treated subjects (26/105, 25%).

The preclinical data and clinical data from volunteers in the three Phase 1 trials showed no evidence of a pro-thrombotic effect of idarucizumab. The safety of idarucizumab is well documented in these volunteers (three Phase 1 studies 1321.1, 1321.2 and 1321.5) and to-date, no dose-related adverse events or serious adverse events were reported to be causally attributed to idarucizumab.

The review notes that the Risk Management Plan (RMP) submitted for this idarucizumab application does not contain a REMS proposal (b) (4)

. The review comments, "The applicant proposes routine risk management measures including routine pharmacovigilance activities with signal detection and evaluation, periodic written reports covering ongoing clinical trials, and annual post-marketing experience. The applicant did not propose any non-REMS materials in the RMP."

The review noted the inclusion in the current draft labeling of Warnings and Precautions for the risks of thrombotic events that may occur secondary to the patient's underlying disease state when dabigatran is discontinued to initiate therapy with idarucizumab, risk of hypersensitivity in patients with known hypersensitivity (e.g., anaphylactoid reaction) to idarucizumab or to any of the excipients weighed against the potential benefit of such an

emergency treatment; and risk of treating a patient with Hereditary Fructose Intolerance with idarucizumab which contains 4 grams of sorbitol as an excipient.

Considering the presentation of one idarucizumab dose (5 g) consisting of 2 separate vials of 2.5 g each, the review commented on a potential risk for medication errors of under dosing with use of one vial (2.5 g) instead of the indicated 2 vials. Upon questioning about the presentation the applicant responded that the formulation had been studied only as two separate vials (2.5 g per vial). (b) (4)

The REMS Review concluded:

The risks for idarucizumab include thrombotic events (of a patients underlying disease) when dabigatran therapy is discontinued and when idarucizumab reversal anticoagulant treatment is initiated, and potential hypersensitivity reactions to idarucizumab. The DRISK and the DHP concurred that a REMS is not a needed to ensure the benefits outweigh the risks for risk management of idarucizumab. The DHP and the DRISK agreed that prescribers (i. e., emergency physicians, surgeons, hematologists, oncologists, internists) are informed on the serious risks associated with discontinuation of dabigatran treatment (Pradaxa labeling includes a BOX WARNING) when initiating an antidote for reversal of the anticoagulant effect of dabigatran. The DHP and DRISK concurred that the reported adverse events/reactions do not appear to be causally attributed to idarucizumab.

Office of Prescription Drug Marketing and Promotion (OPDP):

The Office of Prescription Drug Marketing and Promotion (OPDP) has reviewed and provided comments on the sponsor's proposed promotional materials for product launch. (See letters dated 9/3/2015 and 9/21/2015).

Division of New Drug Bioequivalence Evaluation (DNDBE)/Office of Study Integrity and Surveillance (OSIS):

The Office of Study Integrity and Surveillance (OSIS) inspected the bioanalytical portions of studies 1321.1, 1321.2, and 1321.5 (b) (4). (See OSIS Review by G. Mahadevan, PhD, 9/4/2015). The review made the following observations:

- Observation 1: (b) (4)
- Observation 2: (b) (4)
- Observation 3: (b) (4)
- Observation 4: (b) (4)

The inspection observations were communicated to the applicant through Form FDA 483 and the firm responded adequately to Observation 1. For Observation 2 the review stated that (b) (4)

(b) (4)

The review

provided the following recommendations:

Recommendations:

- The DHP reviewers should evaluate the impact of non-reproducibility and specificity (confirmatory cut point) of confirmatory assay to detect anti-drug antibodies against idarucizumab for all three studies.
- Following the evaluation of the inspectional findings and the firm's response, we recommend that the analytical data for ADA in studies 1321.1, 1321.2, and 1321.5 be accepted for Agency review if the non-reproducibility and specificity of the confirmatory assay did not impact the study outcome.

Division of New Drug Bioequivalence Evaluation (DNDBE)/Office of Study Integrity and Surveillance (OSIS):

The Office of Study Integrity and Surveillance (OSIS) inspected the clinical portions of studies 1321.1, 1321.2, and 1321.5 at Laboratory Menal GmbH, Emmendingen, Germany. (See OSIS Review by G. Mahadevan, PhD, 9/3/2015). The review indicates that the inspection of the clinical portion of the listed studies was conducted by Barbara Carmichael (ORA, FLA-DO) during July 20-23, 2015. The review stated, "At the conclusion of the inspection, no significant issues were observed and no Form FDA 483 was issued. However, the data audit uncovered sponsor-requested repeat analysis of 501 samples for 22 subjects in study # 1321.2. The repeat analysis for blood coagulation parameters such as activated partial thromboplastin time (aPTT), thrombine time (TT), and diluted thrombin time (ANTI-FIIa) was performed for these samples because the pre-dose clotting time was higher than the acceptable upper limit of normal." The review comments that the firm was not able to identify a root cause for the problem. The review recommendations state:

Recommendations:

- The DHP medical reviewer should evaluate the impact of the repeat analysis of the 501 samples in study 1321.2.
- Following the evaluation of the inspectional findings and the EIR, I recommend that the clinical data from studies 1321.1 and 1321.5 be accepted for Agency review. The data from study 1321.2 should be accepted for Agency review if the medical officer determines that the repeated samples didn't impact the integrity of the data.

Division of New Drug Bioequivalence Evaluation (DNDBE)/Office of Study Integrity and Surveillance (OSIS):

The Office of Study Integrity and Surveillance provided a review (S.S. Nkiah, 6/12/2015) that recommended accepting data without an on-site inspection for (b) (4)

(b) (4) and SGS Life Science Services Clinical Research Clinical Pharmacology Unit (in Antwerpen, Belgium) based on that a recently completed inspection of SGS Life Science Services Clinical Research Clinical Pharmacology Unit had an outcome of No Action Indicated (NAI) and although recent inspection of (b) (4) had an outcome of Voluntary Action Indicated (VAI) based on the nature of the findings an inspection was not needed.

CDTL Reviewer comment: Regarding the OSIS recommendations that DHP should evaluate the impact of unexplained repeat analysis of samples in study 1321.2 on the integrity of the data and of non-reproducibility and specificity (confirmatory cut point) of confirmatory assay for anti-drug antibodies against idarucizumab in all three studies (1321.1, 1321.2, and 1321.3) on the study outcome, it is not clear to me that such a sensitivity analysis can be done from a clinical perspective with the available data. Strong consideration should be given to Clinical Pharmacology assessment of these recommendations with regard to interpretation of the study pharmacokinetic and pharmacodynamic results.

12. Labeling

Draft labeling is being developed in discussions with the entire review team. Current draft labeling with comments and recommended edits is included as an attachment in the Clinical Review (Dr. A. Dmytrijuk, 8/27/2015).

Important recommendations for the label include:

- Wording of the indication should take into consideration that efficacy based on a clinical endpoint (e.g., bleeding, significant morbidity or mortality) has not been established. The urgent use clinical setting for use of idarucizumab and the serious conditions of patients receiving the drug make a well-controlled clinical trial not feasible. Therefore, for efficacy approval rests on understanding of the mechanism of action of idarucizumab, which is a targeted monoclonal antibody, and assessment of effects on pharmacodynamic (i.e., clinical laboratory) parameters that reflect anticoagulant activity of dabigatran.
- Adverse reactions listed in the label should reflect events in the studies in normal subjects as well as those in patients.
- The results for Study 1321.3 should be reported for the completed 123 patients who have been treated thus far (b) (4)
- Because the pharmacokinetic and pharmacodynamics results indicate that some patients with high dabigatran levels may require larger amounts of idarucizumab to sustain reversal of pharmacodynamics effects, consideration should be given to including information regarding possible administration of a second 5 g dose of idarucizumab in these patients.

The draft labeling was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) (T. McMillan, PharmD, final signature 8/3/2015). The review examined the Prescribing Information (PI), carton labeling, container labels, (b) (4) and provided a detailed list of recommendations to improve the labeling from a medication error perspective.

The Quality Review recommended that the label should specify: store in a refrigerator at 2-8°C; do not freeze; do not shake; protect from light. These recommendations should be included in the labeling.

13. Recommendations/Risk Benefit Assessment

Recommendations on Benefit-Risk Assessment are included in the Clinical Review (A. Dmytrijuk, M.D., 8/27/2015). The assessment is reproduced below:

Benefit-Risk Summary and Assessment

In two studies in normal healthy volunteers (studies 1321.1 and 1321.2) treated with dabigatran 220mg orally twice daily for 3 days followed by one 220mg dose on day 4 a rapid, dose dependent, reversal of the dabigatran pharmacodynamic effect was observed within 30 minutes of the administration of idarucizumab at doses ranging from 20mg to 8g administered over up to 1 hour or two 2.5g infusions over 5 minutes up to 1 hour apart. The sponsor determined that a 5 g dose or two 2.5 g doses of idarucizumab were the lowest doses of idarucizumab that would be able to neutralize dabigatran for a projected 99% of patients with moderate renal failure from the RE-LY trial, i.e., the pivotal trial used to support the initial marketing application approval for dabigatran. Based on a population pharmacokinetic (PK) model of data from RE-LY the 99th percentiles of trough and peak concentrations of dabigatran in patients with moderate renal failure were 543 and 861 ng/mL. In an interim analysis of an ongoing study (1321.3) in patients who are being treated with dabigatran and require reversal of the dabigatran pharmacodynamic effect due to serious bleeding or the requirement for urgent surgery or procedures idarucizumab administered as two 2.5g intravenous infusions separated by 15 minutes or as a single bolus was able to reverse the pharmacodynamic effect of dabigatran. The reversal of the pharmacodynamic effect by idarucizumab was established using several different coagulation tests such as dilute thrombin time (dTT), thrombin time (TT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT) and activated clotting time (ACT). This pharmacodynamic reversal effect was sustained for a period of at least 24 hours after the last dose of idarucizumab. A dose of 5 g of idarucizumab was calculated by the sponsor to be sufficient for full reversal of dabigatran anticoagulant effect in 99% of patients, based on dabigatran plasma concentrations observed in previous studies of dabigatran used to support its marketing approval. The complete dose of 5 g is administered intravenously as two consecutive infusions over 5 to 10 minutes. The reversal of elevated anticoagulation tests in dabigatran-treated patients is a surrogate for clinical efficacy. The coagulation tests, e.g., aPTT, dTT, pre- and post-treatment, may help the treating physician determine whether reversal of dabigatran has occurred. The data from studies 1321.1 and 1321.2 document the pharmacologic effect and in these normal healthy volunteer studies there were no discontinuations due to adverse events (AEs) and no serious adverse (SAEs). AEs that were observed were of mild-moderate severity. Similarly data from study 1321.3 supports the idarucizumab reversal of the pharmacodynamic anti-coagulant effect of dabigatran in the target population, i.e., when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding. In This study among 123 patients treated with idarucizumab adverse events appeared to be unrelated to treatment. In this study 26 patients died primarily due to complications related to their serious medical conditions, i.e., serious bleeding or causes for the need for urgent surgery/procedures, e.g., trauma or abdominal surgery. The mortality rate was not unexpected in a high risk population with life-threatening events. Two patients developed thrombotic events, these occurred 9 and 13 days after treatment with idarucizumab and in the absence of any antithrombotic treatment. There is no evidence of worsening renal function when idarucizumab is given to patients with renal impairment and full efficacy is

maintained.

The clinical outcome, i.e., a decrease in the risk of bleeding, is difficult to assess. In many cases, bleeding is not visible and cannot be readily measured, e.g. in patients with intracranial hemorrhage (ICH). Other clinical outcomes such as mortality are also significantly confounded by the severity of the underlying clinical situation, e.g., trauma or duration and complications of surgery. A control group to compare outcomes would not be ethical to determine whether mortality rates are impacted by administration of idarucizumab. The target patient population is dabigatran treated patients who require emergency surgery or other invasive intervention where anticoagulation may increase the risk of bleeding, and dabigatran treated patients with life-threatening or uncontrolled bleeding requiring urgent intervention. The sponsor estimates that the incidence of these conditions based on observations in the pivotal trials for dabigatran that the major bleeding rate for patients treated with dabigatran is approximately 3% and is estimated by the sponsor to be <2.5% per year for life-threatening or uncontrolled bleeding during or emergency surgery. Idarucizumab is not intended for use in patients with minor bleeding or other bleeding where standard supportive care is sufficient. It is expected that usage of this drug would be confined to Emergency Departments or other critical care facilities. In summary, 5 g of idarucizumab (administered as 2, 2.5 g infusions separated by 15 minutes) appears to be safe and effective in the reversal of dabigatran anticoagulant pharmacodynamic effect in patients treated with dabigatran who require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. The sponsor should complete study 1321.3 in order to support the approval of idarucizumab for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> Patients treated with dabigatran who require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. Two clinical pharmacology studies (1321.1 and 1321.2) demonstrate that in normal healthy volunteers pre-treated with dabigatran treatment with idarucizumab decreases the pharmacodynamic anticoagulant effect of dabigatran as demonstrated by coagulation tests such as aPTT, TT, dTT. Idarucizumab is a drug specifically targeted to dabigatran which reverses the dabigatran pharmacodynamic effect. It is not targeted 	As with all anticoagulants, patients treated with dabigatran, may be at increased risk for bleeding. Studies 1321.1 and 1321.3 demonstrate that idarucizumab is able to reverse the pharmacodynamic anticoagulant effect of dabigatran. Reversal of the anticoagulant effect of dabigatran is an important clinical benefit in order to decrease the risk of bleeding in patients who may

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	against any other anticoagulant and it is not designed to reverse the pharmacodynamic effect of any other anticoagulant.	require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> Currently there are no approved therapies for the reversal of the anticoagulant effect of dabigatran. The dabigatran product label states that the half-life of dabigatran in healthy subjects is 12 to 17 hours. Recommendations for patients who bleed while receiving dabigatran are based on the mechanism of action of dabigatran, i.e., to administer agents that may possibly overwhelm the inhibited coagulation cascade. Administration of activated prothrombin complex concentrates (PCCs, e.g. FEIBA) or recombinant Factor VIIa, or concentrates of coagulation factors II, IX, or X could be considered, however, these agents have their effects at points in the cascade prior to thrombin. Other, management approaches that could be considered include supportive care with blood products such as fresh frozen plasma, fresh or packed red blood cell (RBCs) transfusions or packed platelet transfusions. However, even with these agents thrombin is a critical factor for coagulation. Dabigatran can be hemodialyzed out of a patient's circulation. Approximately 60% of the drug can be removed over 2-3 hours. (Hankey, G. J. and Eikelboom, J.W.: Dabigatran: a new oral thrombin inhibitor. 2011. Circulation. 123:1436-1450) However, this approach may not be optimal in a situation that requires rapid anticoagulant reversal. 	Idarucizumab is an antidote for dabigatran. Idarucizumab directly binds to dabigatran and reverses dabigatran's pharmacodynamic anticoagulant effect.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	<ul style="list-style-type: none"> Two clinical pharmacology studies (1321.1 and 1321.2) demonstrate that in normal healthy volunteers pre-treated with dabigatran that treatment with idarucizumab decreases the pharmacodynamic anticoagulant effect of dabigatran as demonstrated by coagulation tests such as aPTT, TT, dTT. Additional support for these results comes from one ongoing phase 3 study (1321.3) in patients who are being treated with dabigatran and require reversal of the dabigatran pharmacodynamic effect due to requirement of emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. This study is an open label, multicenter, single arm, safety and efficacy trial in which the sponsor plans to enroll up to adult 300 patients. 	<p>The phase 3 study is ongoing. To date 123 of a planned 300 patients have been enrolled. A decrease in the risk of bleeding is difficult to assess. In many cases, bleeding is not visible and cannot be readily measured, e.g. in patients with intracranial hemorrhage (ICH). Other clinical outcomes such as mortality are also significantly confounded by the severity of the underlying clinical situation, e.g., trauma or duration and complications of surgery. A control group to compare outcomes would not be ethical to determine whether mortality rates are impacted by administration of idarucizumab. The target patient population is dabigatran treated patients who require emergency surgery or other invasive intervention where anticoagulation may increase the risk of bleeding, and dabigatran treated patients with life-threatening or uncontrolled bleeds that require urgent intervention.</p>
<u>Risk</u>	<ul style="list-style-type: none"> The data from studies 1321.1 and 1321.2 document the pharmacologic effect and in these normal healthy volunteer studies there were no discontinuations due to adverse events (AEs) and no serious adverse (SAEs). AEs that were observed were of mild to moderate severity. Similarly data from study 1321.3 supports the 	<p>Study 1321.3 is ongoing. The safety database in patients that have been treated with dabigatran is relatively small, i.e., 123 patients have been treated in study 1321.3 out of a planned 300 patients to be enrolled.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>idarucizumab reversal of the pharmacodynamic anti-coagulant effect of dabigatran in the target population, i.e., when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding. In 123 patients treated with idarucizumab adverse events appeared to be unrelated to treatment. In this study 26 patients died due to their underlying serious medical conditions. The mortality rate was not unexpected in a high risk population with life-threatening events. Two patients developed thrombotic events, these occurred 9 and 13 days after treatment with idarucizumab and in the absence of any antithrombotic treatment. There is no evidence of worsening renal function when this drug is given to patients with renal impairment and full efficacy is maintained.</p>	
<u>Risk Management</u>	<ul style="list-style-type: none"> Idarucizumab is a targeted antidote for dabigatran. 	<p>The sponsor should complete study 1321.3 in order to support the approval of idarucizumab and to enhance the idarucizumab safety database. The purpose for this study is to demonstrate the efficacy and safety of idarucizumab for the reversal of the pharmacodynamic effects of dabigatran in patients who require an urgent surgical procedure or who have serious bleeding. No additional Risk Management Plans are recommended at this time.</p>

Based on the information provided, idarucizumab should be granted Accelerated Approval for the indication for use “in patients treated with dabigatran (Pradaxa®) when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding”.

- Final wording of the labeling should be negotiated with the sponsor taking into consideration the recommendations noted under labeling above.
- A Post-Marketing Requirement to complete and submit the study report for Study .3 should be required. The additional clinical data from the study should strengthen the review finding of adequate demonstration of efficacy of idarucizumab for the intended use as well as provide additional safety data to support the benefit-risk of using idarucizumab for the indication.
- Consideration should be given to encouraging the sponsor to conduct a post-marketing safety study such as recommended by DEPI in an effort to better assess any immunogenicity/anaphylactic risk of idarucizumab.
- The sponsor should be encouraged to consider developing a dosage form such that a single dose of idarucizumab is contained in one vial (5 g) rather than two (2.5 g x 2 vials).
- Currently dabigatran is indicated only for use in adult patients and, consequently, it is anticipated that any use of idarucizumab would be very uncommon, such that pediatric studies would be impractical or impossible. Accordingly, it is reasonable that the sponsor's request for waiver of pediatric studies of idarucizumab be granted. It should be noted, however, that should indications and target patient populations for use of dabigatran as an anticoagulant be expanded to pediatric patients, it may be appropriate to encourage studies of idarucizumab in pediatric patients at that time.

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