

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761025Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 10/15/15

To: Alycia Anderson, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Kathleen Davis, Team Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for PRAXBIND
(idarucizumab) injection, for intravenous use
BLA 761025

In response to your labeling consult request dated May 13, 2015, we have reviewed the draft Package Insert (PI), draft Carton labeling, and draft Container labeling for PRAXBIND (idarucizumab) injection, for intravenous use (Praxbind). This review is based upon the version of the draft PI e-mailed to OPDP on October 9, 2015.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

Package Insert

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
5.2 Re-elevation of Coagulation Parameters	"In a limited number of patients in the clinical program . . ." (emphasis added).	If available, we recommend that the specific numbers of patients in the clinical trials who experienced elevated coagulation parameters be included here, as this would be informative for prescribers.
12.2 Pharmacodynamics	"In a limited number of patients , re-distribution of dabigatran . . ." (emphasis added).	
6.2 Immunogenicity	" As with all proteins there	The phrase "as with all proteins"

	is a potential for immunogenicity with idarucizumab” (emphasis added).	minimizes the risk of immunogenicity associated with Praxbind and is not appropriate for labeling. OPDP recommends deleting “as with all proteins” so that the sentence reads: “There is a potential for immunogenicity with idarucizumab.”
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10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHAEL E CONKLIN
10/15/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 761025
Product Name: Praxbind® (idarucizumab)

PMR/PMC Description: Trial1321.3 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.”

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/19/2015</u>
	Study/Trial Completion:	<u>10/19/2017</u>
	Final Report Submission:	<u>10/19/2018</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Bleeding in patients who are being treated with dabigatran (Pradaxa®) may be serious and potentially life threatening situation. Idarucizumab (Praxbind®) is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding. The bulk of the clinical data submitted in this application is from healthy volunteer trials. Completion and submission of final results for trial 1321.3 will address the uncertainty regarding the applicability of the observed clinical results in healthy volunteers to the ultimate outcome in patients receiving dabigatran treated with Praxbind who experience life threatening or uncontrolled bleeding or need to have an emergency surgery/urgent procedures.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Completion and submission of final results for Trial 1321.3 will address the uncertainty regarding the applicability of the observed clinical results in healthy volunteers to the ultimate outcome in patients receiving dabigatran treated with Praxbind who are experiencing life-threatening or uncontrolled bleeding or a need for emergency surgery/urgent procedures. Thus far, the Applicant has submitted data on 90 of the planned ^{(b)(4)} patients. The data thus far suggest that for the majority of patients, administration of 5g of idarucizumab intravenously to patients treated with dabigatran who presented with dabigatran-related life-threatening or uncontrolled bleeding or who required emergency surgery or urgent procedures will reverse the anticoagulant effect of dabigatran, as measured by ecarin clotting time (ECT) or dilute thrombin time (dTT) in the first 4 hours after administration of 5g idarucizumab. However, in a limited number of patients, between 12 and 24 hours after administration of 5g idarucizumab, elevated coagulation parameters activated partial thromboplastin time (aPTT) or ECT have been observed. Two patients required re-treatment with 5g of idarucizumab with subsequent decrease in coagulation parameters. Therefore completion of the ongoing trial 1321.3 would enhance our understanding of the utility of the Praxbind dosing strategy in patients. In addition, completion of the ongoing trial and analysis of the number of patients who required more than one treatment with idarucizumab could provide additional information which would guide prescribers about the safe and effective use of idarucizumab.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor proposes to complete the ongoing single cohort case series Trial1321.3 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 Etxilate Who Have Uncontrolled Bleeding or Require Emergency Surgery or Procedures, the REVERSE –AD trial.” The sponsor proposes to enroll up to ^{(b)(4)} patients into this trial who have been patients treated with Pradaxa® and require reversal of the anticoagulant effects of dabigatran due to the need for emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Analysis of the number of patients who required re-treatment with idarucizumab, analysis of the idarucizumab reversal of the dabigatran pharmacodynamic anticoagulant effect and analysis of the clinical outcomes of the patients would potentially provide additional information for prescribers about the safe and effective use of idarucizumab.
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALYCIA C ANDERSON
10/13/2015

DIANE V LEAMAN
10/13/2015
For Ann Farrell, MD



FINAL LABEL AND LABELING REVIEW

Date:	October 1 2015
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products <small>Digitally signed by Jibril Abdus samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA ou=People, 0.9.2342.19200300.100.1.1=2000737256, cn=Jibril Abdus samad -S Date: 2015.10.01 10:32:14 -0400</small>
Through:	Frederick Mills, PhD, Quality Reviewer Division of Biotechnology Review and Research IV Frederick C. Mills -S <small>Digitally signed by Frederick C. Mills -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000737256, cn=Frederick C. Mills -S Date: 2015.10.02 11:06:20 -0400</small>
Application:	761025/0
Product:	Praxbind [®] (idarucizumab)
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Dates:	February 19; May 28; August 12, 19; September 23 2015

Executive Summary:

The container labels, carton labeling, (b) (4) labeling for Praxbind[®] (idarucizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies identified, mitigated, and resolved. (b) (4) (b) (4) emailed on September 23 2015 in advance of the official submission is acceptable. The container labels and carton labeling submitted on August 19 2015 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 761025 Praxbind[®] (idarucizumab) on December 22 2014 with the final sections submitted on February 19 2015. Table 1 lists the proposed characteristics of Praxbind[®] (idarucizumab).

Table 1: Proposed Product Characteristics of Praxbind[®] (idarucizumab).

Proprietary Name:	Praxbind
Proper Name:	idarucizumab
Indication:	a humanized monoclonal antibody fragment (Fab) indicated in patients treated with Pradaxa [®] when rapid reversal of the anticoagulant effects of dabigatran is required: <ul style="list-style-type: none">• For emergency surgery/urgent procedures• In life-threatening or uncontrolled bleeding
Dose:	5 g, provided as two separate 2.5 g/50 mL vials
Route of Administration:	Intravenous infusion or bolus injection
Dosage Form:	Injection
Strength and Container-Closure:	2.5 g/50 mL single-dose vial
Storage and Handling:	Store in refrigerator at 2°C to 8°C (36°F to 46°F)

Materials Reviewed:

- Vial Container Labels *
- Carton Labeling *
-  (b) (4)

*Note there are separate vial labels and carton labeling for each drug product manufacturing facility [Boehringer Ingelheim Roxane, Inc Facility (BIRI) and Biberach Facility]

Start of Sponsor Material



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

Applicant's response in Times New Roman font
OBP decisions in Tahoma italics font.

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] **does not conform**.

OBP Request: Relocate the dosage form "Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name.¹ *Applicant revised as requested.*

(2) The name, address, and license number of manufacturer; **does not conform**.

The Applicant/Licensee on the 356h form is the manufacturer per 21 CFR 600.3(t). The Applicant must appear as "Manufactured by:". Additionally, the U.S. License Number must appear with the manufacturer information per 21 CFR 610.61(b).

OBP Request: Revise the manufacturer information to appear as:

Manufactured by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877
U.S. License Number 2006

For the vial container label, only the Applicant/Licensee information is required. Consider omitting any additional manufacturer information.

¹ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 April. Available from:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Applicant's response 8/10/2015 email: The FDA has proposed that the labeling for Praxbind® list the BLA applicant, Boehringer Ingelheim Pharmaceuticals, as the manufacturer, consistent with the definition of "Manufacturer" in 21 CFR 600.3(t). We agree to this FDA recommendation. However we propose to remove the words "Manufactured by" as a preface to this label statement.



OBP Response: Our request to state "Manufactured by" the Applicant/licensee is a standard labeling practice for CDER-regulated BLAs. (b) (4)

, you may remove "Manufactured by". *Applicant revised as requested.*

- (3) The lot number or other lot identification; *conforms.*
- (4) The expiration date; *conforms.*
- (5) The recommended individual dose, for multiple dose containers. *Not applicable, Praxbind is single-dose.*
- (6) The statement: "Rx only" for prescription biologicals; *conforms.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable. Praxbind is enclosed in a carton.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; **does not conform.**

OBP Request:

Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Applicant response is acceptable.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms.*

C. 21 CFR 201.5 Drugs; adequate directions for use; **does not conform**.

The Applicant provided clarification in the PI [REDACTED] (b) (4). We concur with the Division of Medication Error Prevention and Analysis' (DMEPA) recommendation to revise all statements of on the container label and carton labeling [REDACTED] (b) (4) to the following: "Administer 2 vials for complete dose of 5 g".

D. 21 CFR 201.6 Drugs; misleading statements; conforms.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; **does not conform**.

OBP Requests:

Remove the [REDACTED] (b) (4) as this is intervening matter per 21 CFR 201.10(a). *Applicant revised as requested.*

Ensure the font size of the proper name "idarucizumab" is at least half the size of the proprietary name and has prominence commensurate as per 21 CFR 201.10(g)(2). *Applicant revised as requested.*

F. 21 CFR 201.15 Drugs; prominence of required label statements.; **does not conform**.

The labeling prominently displays [REDACTED] (b) (4). Although this is an accurate statement, there is potential for misinterpretation that this product [REDACTED] (b) (4). We concur DMEPA's with recommendation to remove this statement from the principal display panel. *Applicant revised as requested.*

OBP Requests:

Delete [REDACTED] (b) (4) to avoid misinterpretation that this product [REDACTED] (b) (4). *Applicant revised as requested.*

Revise the strength statement such that the strength per total volume is more prominent than the strength per mL by decreasing the font and relocating the strength per mL (50 mg/mL) to appear immediately under the strength per total volume (2.5 g/50 mL) wherever presented on the labels and labeling per USP General Chapters <1>. *Applicant revised as requested.*

Remove the statement (b) (4) to avoid misinterpretation that this product (b) (4) and relocate the statement "For Intravenous Use Only" in its place to ensure adequate prominence of the route of administration. *Applicant revised as requested.*

Add "For Single-use Only, Discard Unused Portion" to appear below the the route of administration. *Applicant revised as requested.*

Decrease prominence of Rx only and relocate to the upper right portion of the principal display panel (PDP) where "FOR INTRAVENOUS USE ONLY" appears. *Applicant revised as requested.*

- G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*
- H. 21 CFR 201.25 Bar code; *conforms.*
- I. 21 CFR 201.50 Statement of identity; *conforms.*
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- K. 21 CFR 201.55 Statement of dosage; *conforms.*
- L. 21 CFR 201.100 Prescription drugs for human use; **does not conform.**

OBP Request: Revise the list of ingredients to include the amounts and place in alphabetical order to comply with USP <1051> Labeling of Inactive Ingredients. The statement should appear as:

Each 50 mL vial contains 2.5 g of idarucizumab, acetic acid glacial (x mg), polysorbate 20 (x mg), sodium acetate trihydrate (x mg), sorbitol (x mg) and water for injection.
Applicant revised as requested.

Applicant's response in Times New Roman font
OBP decisions in Tahoma italics font.

II. Carton

A. 21 CFR 610.61 Package Label:

- a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; **does not conform.**

OBP Request: OBP Request: Relocate the dosage form "Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name.²
Applicant revised as requested.

- b) The name, addresses, and license number of manufacturer; **does not conform.**

The Applicant/Licensee on the 356h form is the manufacturer per 21 CFR 600.3(t). The Applicant must appear as "Manufactured by:". Additionally, the U.S. License Number must appear with the manufacturer information per 21 CFR 610.61(b).

OBP Request: Revise the manufacturer information to appear as:

Manufactured by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877
U.S. License Number 2006

Currently the proposed labeling lists the Applicant as the distributor and states " (b) (4) ". If you propose to include this information on the labeling, cite the regulations you are attempting to fulfill.

² See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 April. Available from:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Applicant's response 8/10/2015 email: The FDA has proposed that the labeling for Praxbind[®] list the BLA applicant, Boehringer Ingelheim Pharmaceuticals, as the manufacturer, consistent with the definition of "Manufacturer" in 21 CFR 600.3(t). We agree to this FDA recommendation. However we propose to remove the words "Manufactured by" as a preface to this label statement.



OBP Response: Our request to state "Manufactured by" the Applicant/licensee is a standard labeling practice for CDER-regulated BLAs. (b) (4)

you may remove "Manufactured by". Additionally, you propose to include the Country of Origin as required by U.S. Customs and Border Protection. Revise "(b) (4)" to "Product of Germany". *Applicant revised as requested.*

- c) The lot number or other lot identification; *conforms.*
- d) The expiration date; *conforms.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms.*
- f) The number of containers, if more than one; *conforms.*

However we concur with DMEPA's recommendation to revise the statement to "Net quantity- Contains 2 vials each containing 2.5 g/50 mL".

- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight,

(5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.

h) The recommended storage temperature; *conforms*.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*

o) The adjuvant, if present; *not applicable*

p) The source of the product when a factor in safe administration; *not applicable*

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; **does not conform**.

OBP Request: Add the statement "No U.S. standard of potency to the side panel near the list of ingredients.
Applicant revised as requested.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. Not applicable.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Praxbind (idarucizumab) is a monoclonal antibody.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor:

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated; **does not conform**.

Currently the proposed labeling lists the Applicant as the distributor and states " (b) (4) ". See request above for 21 CFR 610.61. *Applicant revised the manufacturer information as requested above.*

E. 21 CFR 610.67 Bar code label requirements; *conforms*

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35], *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; **does not conform**.

The preparation and administration instructions for use required clarification from DMEPA and DHP regarding the following:

- Can Praxbind be infused via the vial or injected via syringe?
- Is there a time interval between each infusion.
- What is the rate of administration for each method of infusion.

The Applicant provided clarification in the PI (b) (4). We concur with DMEPA's recommendations to update the proprietary name, (b) (4), and removal of trailing zeroes. *Applicant revised as requested.*

(b) (4)
OBP recommends the rate of administration appear in the labeling to provide clear instructions for HCPs per 21 CFR 201.5 and 21CFR201.57(c)(3). However, OBP defers to the Clinical Team on resolution of this issue. Additionally, we note DMEPA defers to the Clinical Team for the appropriateness (b) (4).

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] **does not conform**.

OBP Requests:

Remove (b) (4) as this is intervening matter per 21 CFR 201.10(a).
Applicant revised as requested.

Ensure the font size of the proper name "idarucizumab" is at least half the size of the proprietary name and has prominence commensurate as per 21 CFR 201.10(g)(2). *Applicant revised as requested.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; **does not conform**.

The labeling prominently displays “ (b) (4) ”. Although this is an accurate statement, there is potential for misinterpretation that this product (b) (4) . We concur with DMEPA’s recommendation to remove this statement from the principal display panel. *Applicant revised as requested.*

OBP Requests:

Revise the strength statement such that the strength per total volume is more prominent than the strength per mL by decreasing the font and relocating the strength per mL (50 mg/mL) to appear immediately under the strength per total volume (2.5 g/50 mL) wherever presented on the labels and labeling per USP General Chapters <1>. *Applicant revised as requested.*

Remove the statement “ (b) (4) ” to avoid misinterpretation that this product (b) (4) and relocate the statement “For Intravenous Use Only” in its place to ensure adequate prominence of the route of administration. *Applicant revised as requested.*

Add “For Single-use Only, Discard Unused Portion” to appear below the the route of administration. *Applicant revised as requested.*

Decrease prominence of Rx only and relocate to the upper right portion of the principal display panel (PDP) where “FOR INTRAVENOUS USE ONLY” appears. *Applicant revised as requested.*

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.
However we concur with DMEPA’s recommendation to revise the statement to Net quantity- Contains 2 vials each containing 2.5 g/50 mL. *Applicant revised as requested.*

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; **does not conform**.

OBP Request: Revise the list of ingredients to include the amounts and place in alphabetical order to comply with USP <1051> Labeling of Inactive Ingredients. The statement should appear as:

Each 50 mL vial contains 2.5 g of idarucizumab, acetic acid (x mg), polysorbate 20 (x mg), sodium acetate trihydrate (x mg), sorbitol (x mg) and water for injection.

Applicant revised as requested.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant's responses were acceptable.

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

B. Carton Labeling

1. Delete "(b) (4)". This product will only be administered in a clinical setting.

C. Container Label

1. Revise the orientation of the side panel so that it is displayed horizontally like the PDP.



Conclusions

The container labels, carton labeling, (b) (4) for Praxbind® (idarucizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies identified, mitigated, and resolved. (b) (4) submitted on September 23 2015 in advance of the official submission is acceptable. The container labels and carton labeling submitted on August 19 2015 are acceptable (see below).



2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Recommendation for Postmarketing Clinical Safety Study

Date:	15 September 2015
Reviewer(s):	Kate Gelperin, MD, MPH Division of Epidemiology 1 (DEPI-1)
Team Leader	Steve Bird, PharmD, PhD, MS DEPI-1
Division Director	Cunlin Wang, MD, PhD DEPI-1
Drug Name(s):	Idarucizumab (PRAXBIND)
Subject	Recommendation for postmarketing clinical safety study
Application Type/Number:	New BLA / 761025
Applicant/sponsor:	Boehringer Ingelheim Pharmaceuticals
OSE RCM #:	2014-2601

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EXECUTIVE SUMMARY

This memo follows a request from the Division of Hematology Products (DHP) at the WRAP-UP meeting for BLA 761025 on 11 September 2015 that DEPI will 1) document our concerns with the difficulty for monitoring the safety of idarucizumab in the postmarket setting and 2) recommend a target sample size for a PMR clinical safety study. DHP asked that DEPI document our rationale for the sample size.

Idarucizumab may be approved soon based on a clinical trials program with only 124 patients in a prospective one-arm observational study (Study 1321.3; target enrollment is 300 patients per initial protocol). This drug will be indicated for patients taking dabigatran who need immediate reversal because they 1) have a major hemorrhage or 2) require emergency surgery.

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).

1 INTRODUCTION

Idarucizumab may be approved soon based on a clinical trials program with only 124 patients in a prospective one-arm observational study (Study 1321.3; target enrollment is 300 patients per initial protocol). This drug will be indicated for patients taking dabigatran who need immediate reversal because they 1) have a major hemorrhage or 2) require emergency surgery.

As noted in the FDA Guidance on *Premarketing Risk Assessment*, “products intended for life-threatening and severely debilitating diseases are often approved with relatively small safety databases” and “relatively greater uncertainty remains regarding their adverse effects.”¹ In such

¹ FDA/CDER/CBER Guidance for Industry: *Premarketing Risk Assessment* March 2005; accessed 14 September 2015; <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126958.pdf>

situations, effective postmarketing safety data collection is essential to inform clinical decision-making and appropriate patient selection.

In Study 1321.3 thus far, there has been a 20% mortality rate, likely due to the underlying indication. Postmarketing data will be very challenging to interpret as a result of this underlying comorbidity. Since atrial fibrillation is a common condition in elderly patients and the potential for idarucizumab use is considerable, it's possible that 300 patients may not be sufficient in the context where postmarketing spontaneous reports from routine pharmacovigilance will be extremely challenging to interpret. Potentially, most major hemorrhage cases reported with dabigatran in FAERS may now be accompanied by exposure to idarucizumab.

The safety concerns to date are immunogenicity, thrombotic events (transient increased risk of thrombosis due to the reversal), and hypersensitivity reactions – although it's challenging to understand the true scope of any safety concern with only 124 patients enrolled to date. There is a need for additional clinical safety data post-approval. The sponsor has been able to enroll 90 patients in the last quarter in Study 1321.3 so enrollment doesn't seem to be an issue.

A decision was made at the WRAP-UP meeting for BLA 761025 on 11 September 2015 that DEPI and DPV will write brief memos to 1) document our concerns with the difficulty for monitoring the safety of this drug in the postmarket setting and 2) recommending a target sample size that DHP will take into consideration. DHP asked that DEPI document our rationale for the sample size we recommend.

2 MATERIALS CONSIDERED FOR THIS REVIEW

- Boehringer Ingelheim 4-Month Safety Update Report; Idarucizumab (BI 655075); Document Number c03603109-01; Date of Report: 17 June 2015.
- Andrew Dmytrijuk, MD; FDA/CDER/OND/DHP Clinical Review BLA 761025; Idarucizumab (Praxbind) Humanized Monoclonal Antibody Fragment for Intravenous Infusion; Date of Review: 10 August 2015.
- Boehringer Ingelheim Integrated Summary of Clinical Safety (ISS); Idarucizumab (BI 655075); Document Number c03076696-01; Date of Report: 29 January 2015.
- Boehringer Ingelheim Risk Management Plan; Idarucizumab (Praxbind); Document Number s00018805-01; Date of Report: 27 January 2015.
- Carolyn L. Yancey, MD; FDA/CDER/OSE/DRISK Risk Evaluation and Mitigation Strategy (REMS) Review; PRAXBIND (Idarucizumab) Injection, for intravenous infusion or injection; Rolling BLA 761-025 complete submission dated 22 February 2015; Date of Review: 13 August 2015.
- Draft label; PRAXBIND® (idarucizumab) injection, for intravenous use; BLA 761025; accessed 14 September 2015 at <A:\Anderson\BLA 761025\BLA761025 Draft Label PRAXBIND.2.1.docx>.

3 IMPORTANT POTENTIAL RISKS

Four “important potential risks” for idarucizumab are identified as follows on page 72 of the Risk Management Plan² submitted by the Sponsor: immunogenicity, hypersensitivity, thrombotic events, and patients with hereditary fructose intolerance.

² Boehringer Ingelheim Risk Management Plan; Idarucizumab (Praxbind); Document Number s00018805-01; Date of Report: 27 January 2015

All of these four potential risks are described to some extent in the current draft labeling for idarucizumab. Regarding hypersensitivity, there is a Warning and Precaution in the highlights section that states the following: “Hypersensitivity reactions: Discontinue administration and evaluate. (5.3)”, and refers to the Warning and Precaution in section 5.3, as follows:

5.3 Hypersensitivity Reactions

There is insufficient clinical experience with PRAXBIND in patients to evaluate risk of hypersensitivity to idarucizumab. In clinical studies adverse events possibly indicative of hypersensitivity reactions where a possible relationship could not be excluded were reported [see Adverse Reactions (6.1)]. The risk of using PRAXBIND in patients with known hypersensitivity (e.g., anaphylactoid reaction) to idarucizumab or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment. If an anaphylactic reaction or other serious allergic reaction occurs, immediately discontinue administration of PRAXBIND and institute appropriate treatment.

Also described in the current draft label are preclinical data which show that many patients have pre-existing antibodies with cross-reactivity to idarucizumab, as follows:

6.2 Immunogenicity

As with all proteins there is a potential for immunogenicity with idarucizumab. Using an electro-chemiluminescence (ECL) based assay, serum samples from 283 subjects (224 treated with idarucizumab) were tested for antibodies cross-reacting with idarucizumab. Pre-existing antibodies with cross-reactivity to idarucizumab were detected in approximately 13 % (36/283) of the subjects. No impact on the pharmacokinetics or the reversal effect of idarucizumab or hypersensitivity reactions were observed in these subjects. Treatment-emergent possibly persisting anti-idarucizumab antibodies with low titers were observed in 4 % (9/224) of the subjects treated with idarucizumab.

The epitope specificity of antibodies to idarucizumab was characterized using probe molecules. (b) (4)

Detection of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to idarucizumab with the incidence of antibodies to other products may be misleading.

Information in the current draft label reflects the limited safety information available to date, especially for events which may not occur commonly with this drug.

4 DISCUSSION

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 "rule of threes" states that, if no events of a particular type (e.g., serious hypersensitivity reactions) are observed in a study of X individuals, "then one can be 95% certain that the event occurs no more often than 3/X. For example, if 500 patients are studied prior to marketing a drug, then one can be 95% certain that any event which does not occur in any of those patients may occur with a frequency of 3 or less in 500 exposed subjects, or that it has an incidence rate of less than 0.006."³ A study of 1000 patients could cap the likely risk around 0.003 (3 in 1000) if no occurrences of an event of interest are observed in that cohort. The so-called "rule of threes" may provide a useful context to consider an optimal target sample size for a postmarketing clinical safety study designed to assess the risk of serious adverse drug reactions with idarucizumab.

To better understand the true benefit for use of idarucizumab, it may also be helpful to conduct an analysis to compare the mortality rates among patients who do and do not receive idarucizumab. This could be implemented by comparing mortality rates among 1) dabigatran exposed patients who have a major hemorrhage / emergency surgery who receive idarucizumab (this trial) versus 2) dabigatran exposed patients who have a major hemorrhage / emergency surgery and do not receive idarucizumab (from historical dabigatran trials). In this context, hemorrhage / surgery cases would need to be matched based on comorbidity, age, and event severity, while blinded to the outcome of mortality. This may provide evidence to help quantify the benefit of idarucizumab on overall mortality.

5 CONCLUSION

The current ongoing clinical safety study 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 it is not observed during the study.

6 RECOMMENDATIONS

- 1) 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.
- 2) DEPI also recommends the sponsor conduct an evaluation to compare mortality rates among 1) dabigatran exposed patients who have a major hemorrhage / emergency surgery who receive idarucizumab (this trial) versus 2) dabigatran exposed patients who have a major hemorrhage / emergency surgery and do not receive idarucizumab (from historical dabigatran trials).

³ Strom B. Sample Size Considerations for Pharmacoepidemiologic Studies. In Strom BL, Kimmel SE, Hennessy S, eds. *Pharmacoepidemiology* (5th edition). Wiley-Blackwell, 2012; pages 52-61.

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/s/

KATE GELPERIN
09/15/2015

STEVEN BIRD
09/15/2015

CUNLIN WANG
09/15/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 4, 2015

TO: Ann Farrell, M.D.
Director
Division of Hematology Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

Xiaohan Cai, Ph.D.
Visiting Associate
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Director (Acting)
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Inspection and EIR Review Memo of [REDACTED] (b) (4)
[REDACTED] covering BLA 761025, Idarucizumab, sponsored by
Boehringer Ingelheim Pharmaceuticals, Inc., USA

At the request of the Division of Hematology Products (DHP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the bioanalytical portions of the following studies:

[REDACTED] (BLA 761025, Idarucizumab sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., USA)

Study #: 1321.1; [REDACTED] (b)(4) 8266-168
Study Title: "Randomized, double-blind, placebo-controlled, Phase 1 study in healthy male volunteers to investigate the safety, tolerability, and pharmacokinetics of single rising doses of BI 655075 (part 1) and to explore the dose of BI 655075 effective to reverse Dabigatran anticoagulant activity (part 2)"

Study #: 1321.2; [REDACTED] (b)(4) 8294-483
Study Title: "Randomized, double-blind, placebo-controlled, two-way crossover phase 1b 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"

Study #: 1321.5; [REDACTED] (b)(4) 8295-792
Study Title: "Randomized, double-blind within dose groups, placebo-controlled, two-way crossover phase I trial in healthy Japanese male volunteers to investigate the safety, tolerability, pharmacokinetics of different doses of BI 655075 (part 1) and to explore the effective dose of BI 655075 to reversal of Dabigatran anticoagulant activity (part 2)"

Analytical Inspection:

The inspection of the analytical portions of the above studies was conducted by scientists from OSIS, Michael Skelly, Ph.D. (DGDBE), Gajendiran Mahadevan, Ph.D. (DNDBE), Kara Scheibner, Ph.D. (DGDBE), and Xiaohan Cai, Ph.D. (DGDBE) on [REDACTED] (b)(4). The inspection included a thorough examination of study records, facilities and equipment, and interviews/discussions with the firm's staff and management.

At the conclusion of the inspection, Form FDA 483 was issued (**Attachment-1**). The firm responded to Form FDA 483 on [REDACTED] (b)(4) (**Attachment-2**). The Form FDA 483, the firm's response to the observations, and our evaluation follow.

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[REDACTED] (BLA 761025, Idarucizumab sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., USA)

(b) (4)

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

(b) (4)

Page 11 - Review of EIR for [REDACTED] (b)(4)
[REDACTED] (BLA 761025, Idarucizumab sponsored by
Boehringer Ingelheim Pharmaceuticals, Inc., USA)

for Agency review if the non-reproducibility and specificity
of the confirmatory assay did not impact the study outcome.

Gajendiran Mahadevan, Ph.D.
DNDBE, OSIS

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Xiaohan Cai, Ph.D.
DGDBE, OSIS

Michael F. Skelly, Ph.D.
DGDBE, OSIS

Final Classification:

VAI: [REDACTED] (b)(4)
FEI: [REDACTED] (b)(4)

E-mail CC:
OSIS/Taylor/Dejernett/Fenty-Stewart/Nkah/Johnson
OSIS/DGDBE/Haidar/Skelly/Choi/Scheibner/Cai
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Mahadevan

CDER/OND/DHP/Farrell/Anderson

Draft: GM 08/15/2015; XC 08/20/2015; MFS 08/24/2015; KAS
09/01/2015
Edit: SHH 09/04/2015

OSI File: [REDACTED] (b)(4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

FACTS: [REDACTED] (b)(4)

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/s/

GAJENDIRAN MAHADEVAN
09/04/2015

KARA A SCHEIBNER
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CAI XIAOHAN
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MICHAEL F SKELLY
09/04/2015

SAM H HAIDAR
09/04/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 3, 2015

TO: Ann Farrell, M.D.
Director
Division of Hematology Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Lead Pharmacologist
Division of New Drugs Bioequivalence Evaluation
Office of Study Integrity and Surveillance

and

Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Review of EIR for Laboratory Menal GmbH, Emmendingen,
Germany covering BLA 761025, Idarucizumab, Boehringer
Ingelheim Pharmaceuticals, Inc., USA

At the request of the Division of Hematology Products (DHP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of the following studies:

Study #: 1321.1
Study Title: "Randomized, double-blind, placebo-controlled, Phase 1 study in healthy male volunteers to investigate the safety, tolerability, and pharmacokinetics of single rising doses of BI 655075 (part 1) and to explore the dose of BI 655075 effective to reverse Dabigatran anticoagulant activity (part 2)"

Study #: 1321.2
Study Title: "Randomized, double-blind, placebo-controlled, two-way crossover phase 1b 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"

Study #: 1321.5
Study Title: "Randomized, double-blind within dose groups, placebo-controlled, two-way crossover phase I trial in healthy Japanese male volunteers to investigate the safety, tolerability, pharmacokinetics of different doses of BI 655075 (part 1) and to explore the effective dose of BI 655075 to reversal of Dabigatran anticoagulant activity (part 2)"

Clinical Inspection:

The inspection of the clinical portion of the above studies was conducted by Barbara Carmichael (ORA, FLA-DO) during July 20-23, 2015 at **Laboratory Menal GmbH, Emmendingen, Germany**. The inspection included a thorough examination of the protocol, protocol amendments, study records, informed consent forms, SOPs, IRB approvals, case report forms, and interviews/discussions with the firm's staff and management.

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 (**Attachment-1**).

An investigation was conducted by the firm. However, the root-cause for the problem could not be identified and a complete investigation report was not made available to Investigator Carmichael during the inspection. The sponsor-requested repeat analysis for the 501 samples are tabulated below for subjects 601, 204, 503, 501, 301, 302, 303, 304, 305, 306, 307, 104, 105, 106, 101, 102, 103, 201, 202, 203, 205, and 701.

Subject #	Visit #	Number of Samples	Analyte
601	2	18	aPTT
204	3	21	TT
503	2	18	TT
501	3	18	TT
301	2	16	ANTI-FIIa
302	2	16	ANTI-FIIa
303	2	16	ANTI-FIIa
304	2	16	ANTI-FIIa
301	3	16	ANTI-FIIa
302	3	16	ANTI-FIIa
303	3	16	ANTI-FIIa
304	3	16	ANTI-FIIa
305	2	16	ANTI-FIIa
306	2	16	ANTI-FIIa
307	2	16	ANTI-FIIa
104	2	20	ANTI-FIIa
105	2	20	ANTI-FIIa
106	2	21	ANTI-FIIa
101	3	21	ANTI-FIIa
102	3	21	ANTI-FIIa
103	3	21	ANTI-FIIa
201	3	21	ANTI-FIIa
202	3	21	ANTI-FIIa
203	3	21	ANTI-FIIa
204	3	21	ANTI-FIIa
205	3	21	ANTI-FIIa
701	2	21	ANTI-FIIa

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.

Gajendiran Mahadevan, Ph.D.
DNDBE, OSIS

Final Classification:

NAI: Laboratory Menal GmbH, Emmendingen, Germany
FEI: 3008655451

E-mail CC:
OSIS/Taylor/Dejernett/Fenty-Stewart/Nkah/Johnson
OSIS/DGDBE/Haidar/Skelly/Choi
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Mahadevan

CDER/OND/DHP/Farrell/Anderson

ORA/FLA-DO/Sinninger/Carmichael

Draft: GM 08/28/2015
Edit: AD 09/01/2015; CB 09/03/2015

OSI File: BE6890; O:\BE\EIRCOVER\761025.ida.boe.Menal
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Laboratory Menal GmbH, Germany /BLA 761025_Idarucizumab

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/s/

GAJENDIRAN MAHADEVAN
09/03/2015

ARINDAM DASGUPTA
09/03/2015

CHARLES R BONAPACE
09/03/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: July 30, 2015

Requesting Office or Division: Division of Hematology Products

Application Type and Number: BLA 761025

Product Name and Strength: Praxbind (Idarucizumab)
Injection
2.5 g/50mL
(50 mg/mL)

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Submission Date: December 22, 2014, February 19, 2015, and May 29, 2015

OSE RCM #: 2014-2602

DMEPA Primary Reviewer: Teresa McMillan, PharmD

DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the Prescribing Information (PI), carton labeling, container labels, (b) (4) for Praxbind (Idarucizumab) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products (DHP) requested this review as part of their evaluation of BLA 761025 for Praxbind.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the Prescribing Information (PI), carton labeling, container labels, (b) (4) identified the following areas that could be improved from a medication error perspective.

- The carton labeling and container labels contain the (b) (4) statement. We recommend removal of this statement (b) (4). Also, the net quantity and total concentration statements could be improved to avoid confusion.

- (b) (4)

In addition, we note that the recommended dose for this product is 5 grams, provided in two vials, each containing 2.5 g/50 mL. From a medication error perspective, we are concerned that healthcare practitioners may not administer the entire dose as packaged due to the fact that one dose is comprised of two separate vials. Therefore, under doses may occur. We have provided recommendations to the labels and labeling to help

minimize this risk. However, these recommendations alone may not be sufficient to minimize under doses. We defer to the clinical team to determine if the applicant should consider developing one single dose 5 gram vial as a post marketing commitment and/or requirement.

Additionally, according to the DHP's clinical team, it appears that in the clinical studies, the product was administered with an interval of 15 minutes in between the vials and never administered as one vial immediately after another. Thus, it also is unclear if the bolus administration option is compatible with any syringe for administration of this product. However, one of the administration options in the Dosage and Administration section of the PI recommends a bolus injection administration, in which a dose of 2.5 g withdrawn to a syringe is immediately followed by another 2.5 g. We defer to the clinical team to determine the appropriateness of including the time interval for the bolus administration option in the D&A section of the PI and to determine the compatibility of syringe types to be used for bolus administration of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels and labeling to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Revise all instances of the "TRADENAME" to the proprietary name PRAXBIND.
2. If appropriate, consider adding the time interval for the bolus injection administration option for this product in the Dosage and Administration section.

4.2 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM

We recommend the following be implemented prior to approval of this BLA:



B. Carton Labeling (All)

1. Relocate the “Rx only” statement to where the “FOR INTRAVENOUS USE ONLY” statement is located.
2. Remove the statement [REDACTED] (b) (4) to avoid misinterpretation that this product [REDACTED] (b) (4) and relocate the statement “For Intravenous use” in its place to ensure adequate prominence of the route of administration.
3. Place the following statement under the “For Intravenous Use Only”:
“For Single Use Only. Discard after use”
4. Decrease the font and relocate the concentration of (50 mg/mL) immediately under the total drug content (2.5 g/50 mL) wherever presented on the labels and labeling per USP’s Chapter <1>. For example:

2.5 g/50 mL
(50 mg/mL)

5. Revise all statements of [REDACTED] (b) (4) to the following:
Administer 2 vials for complete dose of 5 g
6. Revise the dosage statement to the following:
For single use only. See package insert for Full Prescribing Information for dosage and administration. Discard unused portion.
7. Revise the net quantity statement to the following:
Net quantity- Contains 2 vials each containing 2.5 g/50 mL

8. Revise the statements [REDACTED] (b) (4) statements on the top panel where the lot number and expiration date is located to the following:

Administer 2 vials for complete dose of 5 g

See package insert for Full Prescribing Information for dosage and administration.

9. Delete the [REDACTED] (b) (4) statement on the side panel as this product will only be administered in a clinical setting.

10. Revise the statements [REDACTED] (b) (4) on the opening flap inside panel to the following:

See package insert for Full Prescribing Information for dosage and administration and Administer 2 vials for complete dose of 5 g

11. Delete the following statements from the opening flap inside panel:

[REDACTED] (b) (4)

C. Container Labels (All)

1. See comments B1 through B6.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Praxbind that Boehringer Ingelheim Pharmaceuticals, Inc. submitted on April 19, 2015.

Table 2. Relevant Product Information for Praxbind	
Initial Approval Date	N/A
Active Ingredient	Idarucizumab
Indication	For patients treated with Pradaxa when rapid reversal of the anticoagulant effects of dabigatran is required: <ul style="list-style-type: none">• For emergency surgery/urgent procedures• In life-threatening or uncontrolled bleeding
Route of Administration	Intravenous
Dosage Form	Solution for Intravenous Injection
Strength	2.5 g/50 mL (50 mg/mL)
Dose and Frequency	5 grams administered consecutively as two 2.5 gram vials as bolus injection or intravenous infusion. The safety and effectiveness of repeat treatment with Praxbind has not been established.
How Supplied	Carton including 2 single use vials each containing 2.5 grams of Idarucizumab
Storage	2°C -8°C (36°F-46°F) and should be kept in the outer carton to protect from light until the time of use.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Praxbind labels and labeling submitted by Boehringer Ingelheim Pharmaceuticals, Inc. on April 19, 2015 and May 29, 2015.

- Container label
- Carton labeling

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
07/30/2015

YELENA L MASLOV
08/03/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 12, 2015

TO: Division of Hematology Products (DHP)

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

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: BLA 761025

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected SGS Life Science Services Clinical Research Clinical Pharmacology Unit and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).

OSIS recently inspected (b) (4) and the inspectional outcome from the analytical site was classified as Voluntary Action Indicated (VAI). Although, the last inspection was classified as a VAI, based on the nature of the findings from our last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.

Requested Sites Inspection

Facility Type	Facility Name	Facility Address
Clinical	SGS Life Science Services Clinical Research Clinical Pharmacology Unit	Antwerpen; Lange Beeldekensstraat 267; B-2060 Antwerpen , Belgium
Analytical	(b) (4)	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
06/12/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 761025

Application Type: New BLA

Name of Drug/Dosage Form: Praxbind (idarucizumab), 2.5gm/50mL (50 mg/mL)

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Date: February 19, 2015

Goal Date: October 19, 2015

1. Regulatory History and Applicant's Main Proposals

Boehringer Ingelheim Pharmaceuticals, Inc. submitted an original Biologics License Application (BLA) for idarucizumab, which is a humanized monoclonal antibody fragment (Fab) specific neutralizing agent for dabigatran that can rapidly reverse the anticoagulant effect of dabigatran. The proposed indication for idarucizumab is for patients treated with Pradaxa when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.

On June 16, 2014, idarucizumab was granted Breakthrough Designation for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required.

On October 14, 2014, idarucizumab was granted Rolling Review. On December 22, 2104, Boehringer Ingelheim submitted the first portion, nonclinical information, of their BLA. The final and complete submission was submitted and received on February 19, 2015.

Boehringer Ingelheim Pharmaceuticals, Inc. intends to use idarucizumab for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Under Indications and Usage, (1) should be placed after the first paragraph and before the colon, instead of at the end of the last bullet.*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment: *The drug product name is not listed, instead TRADENAME is typed.*

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *The product name is not listed, instead TRADENAME is typed.*

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Bullet "For intravenous use only" and delete the ".0" in 5.0g.*

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *"None" does not need to be bulleted.*

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Bold "www.fda.gov/medwatch."*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Not Right Justified.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ALYCIA C ANDERSON
05/01/2015

MARA B MILLER
05/01/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761025	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Praxbind Established/Proper Name: idarucizumab Dosage Form: Injection Strengths: 2.5gm/50mL (50 mg/mL)		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: February 19, 2015 Date of Receipt: February 19, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: October 19, 2015		Action Goal Date (if different):
Filing Date: April 20, 2015		Date of Filing Meeting: March 20, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Idarucizumab is indicated in patients treated with Pradaxa [®] when rapid reversal of the anticoagulant effects of dabigatran is required: For emergency surgery/urgent procedures and In life-threatening or uncontrolled bleeding		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i><i>The product is a Qualified Infectious Disease Product (QIDP)</i><i>A Tropical Disease Priority Review Voucher was submitted</i><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): 112278

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	(b) (4) The PSP has been submitted with the BLA.
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Division of Cardiovascular and Renal Products
<i>If yes, specify consult(s) and date(s) sent:</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 14, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-BLA
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 20, 2015

BACKGROUND: Boehringer Ingelheim Pharmaceuticals, Inc. submitted an original Biologics License Application (BLA) for idarucizumab, which is a humanized monoclonal antibody fragment (Fab) specific neutralizing agent for dabigatran that can rapidly reverse the anticoagulant effect of dabigatran. The proposed indication for idarucizumab is for patients treated with Pradaxa when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.

On June 16, 2014, idarucizumab was granted Breakthrough Designation for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required.

On October 14, 2014, idarucizumab was granted Rolling Review. On December 22, 2104, Boehringer Ingelheim submitted the first portion, nonclinical information, of their BLA. The final and complete submission was submitted and received on February 19, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alycia Anderson	Y
	CPMS/TL:	Patricia Garvey (TL)	Y
Cross-Discipline Team Leader (CDTL)	Kathy Robie Suh		Y
Division Director/Deputy	Ann T. Farrell		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Andrew Dmytrijuk	Y
	TL:	Kathy Robie Suh	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial</i>)	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Pharmacology	Reviewer:	Martina Sahre	Y
	TL:	Rajnikanth Madabushi	Y
Biostatistics	Reviewer:		
	TL:	Yuan Li Shen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Place	N
	TL:	Pedro Del Valle	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Lixin Xu	Y
	TL:	Chana Fuchs	Y
Biopharmaceutics	Reviewer:		
	TL:		
Quality Microbiology	Reviewer:	Patricia Hughes	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Teresa McMillan	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Jeffrey Florian, Dinko Rekić		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application does not raise significant safety or efficacy issues.
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIostatistics</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
IMMUNOGENICITY (protein/peptide products only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
New Molecular Entity (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If no, was a complete EA submitted?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If EA submitted, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Quality Microbiology</u>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: EERs are no longer submitted for the BLAs according to the RBPM.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>None</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, MD</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): May 15, 2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60

<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALYCIA C ANDERSON
04/20/2015

PATRICIA N GARVEY
04/20/2015