CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761025Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, M.D.
Subject	Office Director Summary Review
BLA #	761025
Applicant Name	Boehringer Ingelheim Pharmaceuticals
Date of Submission	02/19/2015
PDUFA Goal Date	10/19/2015
Proprietary Name / Established (USAN) Name	Praxbind Idarucizumab
Dosage Forms / Strength	Solution for injection/infusion 2.5 g idarucizumab/50 mL
Proposed Indications	Reversal of the anticoagulant activity of dabigatran for (1) emergency surgery/urgent procedures, and (2) life-threatening or uncontrolled bleeding
Recommended Action for NME:	*Accelerated Approval*

Material Reviewed/Consulted OND Action Package, including:	
Deputy Division Director Review	Edvardas Kaminskas, M.D.
Medical Review	Andrew Dmytrijuk, M.D./Kathy M. Robie Suh, M.D., Ph.D.
Regulatory Project Manager	Alycia Anderson
Pharmacology Toxicology Review	Emily Place, Ph.D., M.P.H./Christopher Sheth, Ph.D.
OBP Review	Tura Camilli, Ph.D./Lixin Xu, M.D., Ph.D./Frederick Mills, Ph.D./Chana Fuchs, Ph.D.
Clinical Pharmacology Review	Martina Sahre, Ph.D./Dinko Rekic, Ph.D./Rajanikanth Madabigatranushi, Ph.D./Jeffrey Florian, Ph.D.
OSIS/DGDBE	Gajendiran Mahadevan, Ph.D./Kara A. Schreiber, Ph.D./Xiaohan Cai, Ph.D./Sam F. Skelly, Ph.D.
CDTL Review	Kathy M. Robie Suh, Ph.D., M.D.
OMEPRM/DMEPA	Teresa McMillan, Pharm.D./Yelena Maslov, Pharm.D.
OPDP	James Dvorsky, Pharm.D.
OSE/DRISK	Carolyn L. Yancey, M.D./Naomi Redd, Pharm.D./Cynthia LaCivita, Pharm.D.
OPE/OSE/DEPI-1	Kate Gelperin, M.D., M.P.H./Steve Bird, Pharm.D./Ph.D., M.S./Cunlin Wang, M.D., Ph.D.

OND=Office of New Drugs
OPE=Office of Pharmacovigilance and Epidemiology
OSE= Office of Surveillance and Epidemiology
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
OSIS=Office of Study Integrity and Surveillance
DNDBE=Division of New Drug Bioequivalence Evaluation
OMEPRM=Office of Medication Error Prevention and Risk Management
DRISK=Division of Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
DEPI-1=Division of Epidemiology 1

1. Introduction

Idarucizumab, a humanized murine monoclonal antibody fragment (Fab) that binds with high affinity to the direct thrombin inhibitor dabigatran, was developed in order to provide reversal of the anticoagulant effect of dabigatran, one of several novel oral anticoagulants (NOACs) that have been approved. Dabigatran was approved in 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of DVT and PE in patients who have been previously treated.

Dabigatran and the other approved NOACs (factor Xa inhibitors rivaroxaban, apixaban, and edoxaban) have been at least as effective, safer, and simpler to use than warfarin. NOAC dosing regimens are simpler, produce more rapid anticoagulation, have fewer drug-drug interactions. In addition, their effect is not influenced by diet and have not required monitoring by coagulation tests. These advantages are offset by the lack of standardized tests that measure the degree of anticoagulation, and the absence of antidotes to reverse anticoagulation in cases of emergency surgery, severe bleeding, or trauma. Idarucizumab was developed to meet the need for a reversal agent to dabigatran.

2. Background

The Applicant addressed the need for a reversal agent to dabigatran by developing a humanized monoclonal antibody with a high affinity for dabigatran, a classic approach pioneered by the developers of an antidote to digoxin (presently marketed as Digibind). The IND was accepted by the Division of Hematology Products on 12/23/2013. Breakthrough therapy designation was granted on 06/16/2014. Proprietary name was granted on 11/17/2014. The BLA was filed on 02/19/2015. Priority review was granted.

Idarucizumab has not been approved for marketing in any jurisdiction.

3. CMC

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761025 for Praxbind (idarucizumab). The data submitted in this application are adequate to support the conclusion that the manufacture of Praxbind is well controlled and leads to a product that is pure and potent. OPQ provided an overall acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 30 months at (b) (4) ºC. No Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps are recommended from an OPQ perspective. There are no issues that preclude approval of this BLA from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

Idarucizumab binds to dabigatran with higher affinity (~300 times higher) than the binding of dabigatran to thrombin. Idarucizumab forms a stable complex with dabigatran to neutralize dabigatran's anticoagulant effects. There is no endogenous target for idarucizumab. Idarucizumab did not affect the activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), direct thrombin inhibitors hirudin and argatroban, vitamin K antagonist warfarin, or heparin.

Pharmacology, safety pharmacology, and toxicology studies were conducted in *in vitro* and *in vivo* models. *In vitro* studies showed that idarucizumab forms complexes with dabigatran and dabigatran metabolites. Three animal models (a mouse intracranial hemorrhage model, a rat tail cut bleeding model, and a pig blunt liver trauma model) demonstrated that idarucizumab results in reversal of the anticoagulant effects of dabigatran and significant reduction of blood loss. Additional data demonstrated that the effects of idarucizumab are in part mediated by increasing fibrin coverage and fibrin masses around damaged subendothelium.

No major target organs of toxicity were identified in rats or monkeys. Since idarucizumab is only intended to be administered in acute situations, genetic toxicology, reproductive and developmental, and carcinogenicity studies were not needed. The Applicant's proposed Pregnancy Category (b) (4) for idarucizumab is acceptable. From a nonclinical perspective, Praxbind may be approved for the proposed indications. No additional nonclinical studies are needed.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted two randomized, placebo-controlled, double-blind Phase 1 studies in healthy volunteers (n=283) that define the pharmacokinetics (PK) of idarucizumab and the effects of idarucizumab on dabigatran PK and clinical coagulation markers. In addition, preliminary clinical data were also available from an ongoing open-label observational Phase 3 study (n=123). These studies demonstrated that there was a dose-dependent reversal of anticoagulant effect of dabigatran in study subjects who received intravenous single or split doses of idarucizumab, ranging from 20 mg to 8 g, administered over periods up to 1 hour or two 2.5 g infusions over 5 minutes up to 1 hour apart following dabigatran administration. The reversal of anticoagulant effect was measured using dilute thrombin time, thrombin time, ecarin clotting time, and activated thromboplastin time (aPTT). The results show that administration of two doses of idarucizumab 2.5 g intravenously 15 minutes apart can reverse and sustain the reversal of the anticoagulant effect of dabigatran for at least 24 hours.

Pharmacokinetics, metabolism, effects of age, sex, and race, the effect of renal impairment, and drug distribution were also defined. There was no difference in the anticoagulation reversal between males and females (limited data, since only 19 of 283 subjects were females), younger (45 – 64 years of age) and older (65 – 80 years of age) subjects, Caucasian and Japanese subjects, and subjects with mild or moderate renal impairment and normal renal function (limited data, since only 20 subjects had renal impairment).

Idarucizumab has no intrinsic pro-thrombotic effect. Re-initiation of dabigatran treatment 24 hours after treatment with idarucizumab resulted in comparable unbound dabigatran concentrations and anticoagulant activity before and after idarucizumab treatment.

Pre-existing antibodies with cross-reactivity to idarucizumab were detected in 13% of subjects. These antibodies were non-specific, with low titers, binding to the C-terminus of the molecule and having no impact on reversal of dabigatran-induced prolongation of coagulation parameters dTT and ECT.

The reviewers concluded that there is sufficient clinical pharmacology information provided in the BLA to support approval of idarucizumab for the reversal of the anticoagulant activity of dabigatran in emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding. No phase 4 study commitments were recommended.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The Clinical review team reviewed the results of the clinical pharmacology trials and the preliminary results of the Phase 3 trial entitled "A Phase III, Case Series Clinical Study of the Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration of 5.0 g of Idarucizumab in Patients Treated with Dabigatran Etexilate Who Have Uncontrolled Bleeding or Require Emergency Surgery or Procedures, the REVERSE-AD Trial". The trial is an open label, multicenter, single-arm, safety and efficacy trial with projected enrollment of up to 300 adult patients. The protocol was amended to include approximately (b) (4) adult patients. The key enrollment criteria are bleeding that requires a reversal agent in the opinion of the physician, or urgent requirement for surgery or an

invasive procedure in patients who must be taking dabigatran. The dose of idarucizumab is fixed at 5 g administered as two 2.5 g doses 15 minutes apart. The maximum reversal of dilute thrombin time (dTT) or ecarin clotting time (ECT) in the 4 hours after idarucizumab administration was the primary efficacy endpoint.

Of the 123 patients in this interim analysis, 66 were bleeding and 57 required urgent surgery. The median age was 77 years (range 48 – 93 years), 40% had moderate or severe renal insufficiency, the median time from last dabigatran dose was 16 hours (range, 1 – 94 hours), and indication for dabigatran treatment was atrial fibrillation in 95% of patients. In the serious bleeding group, 41% presented with gastrointestinal bleeding and 36% with intracranial bleeding. The most common conditions requiring urgent surgery were bone fractures (23%).

A maximal reversal (100%) of dTT was achieved in 98% of bleeding patients and 93% of patients needing urgent surgery. A maximal reversal of ECT was achieved in 89% of bleeding patients and 88% of patients needing urgent surgery. Both dTT and ECT decreased to normal levels within 10 – 30 minutes after idarucizumab administration and were sustained for a period of 24 hours. Reversal of elevated coagulation tests is considered a surrogate for clinical efficacy.

Two 2.5 g doses (for a total of 5 g) were administered to all but a few patients. Two patients received an additional 5 g dose due to elevation of coagulation parameters and re-bleeding, and one received a total of three 5 g doses for the same reasons.

In bleeding patients, time to bleeding cessation was estimated in 73% of patients; in others, the bleeding site could not be identified. Bleeding stopped within 72 hours in 44 of 48 patients; the median time was 9.8 hours. Among patients requiring urgent surgery, intra-operative bleeding status was assessed in 52 patients. Most patients (48/52) had normal hemostasis, 3 had mildly abnormal and 1 had moderately abnormal (controllable) hemostasis. Assessments of hemostasis and of bleeding cessation were subjective; however, these data are useful in considerations of efficacy of the reversal agent. Dabigatran was re-started after idarucizumab treatment in 26% of bleeding patients and 60% of urgent surgery patients.

8. Safety

The safety data base included the healthy volunteer studies (n=283) and the preliminary report on patients with severe bleeding and patients requiring urgent surgery treated with the pre-specified 5 g dose of idarucizumab in the on-going open label, single arm, safety and efficacy trial in which up to (b) (4) patients will be enrolled (n=123). The percentage of healthy volunteers with AEs was the same in the idarucizumab groups and the placebo groups (~25%). Headache, skin irritation and dizziness were more frequent in the idarucizumab group than in the placebo group. Minor bleeding events, such as epistaxis, were more common in the dabigatran pre-treatment group (~2%) than in the idarucizumab treatment group (0.4%). All AEs were assessed as mild.

The patients in the clinical study had conditions requiring anticoagulation as well as numerous comorbidities. All patients can be characterized as having serious medical conditions. In the severe bleeding group, 41% presented with gastrointestinal bleeding, 36% with intracranial bleeding, the remaining had bleeding due to trauma, or intramuscular, retroperitoneal, intra-pericardial, and intra-ocular bleeding; bleeding location could not be identified in one patient. In the urgent surgery group, 23% of patients had bone fractures, 12% gall bladder disease requiring cholecystectomy, 7% had joint wound infection, and 5% had acute appendicitis, small bowel obstruction or bowel perforation.

There were 26 deaths among the 123 patients. Eleven died within 1 day of idarucizumab administration. Deaths were due to cardiovascular events (5), intracranial hemorrhage progression (2), septic shock (2), peritonitis, and respiratory failure. An additional 7 patients died between 1 and 30 days of idarucizumab administration. Causes of death were cardiovascular events (4), intracranial hemorrhage progression, cerebral infarction, and multi-organ failure. An additional 8 patients died between 31 and 106 days of idarucizumab administration. Causes of deaths

were progression of malignant disease (3), pneumonia (2), gastrointestinal hemorrhage, Parkinson's disease and general health deterioration. None of the deaths could be related to idarucizumab administration.

Among serious adverse events were deep vein thrombosis in 2% of patients and pulmonary embolism in 2% of patients; none were on antithrombotic therapy at the time of the event. A total of 84% of patients reported AEs. AEs in >5% of patients were hypokalemia, delirium, constipation, pyrexia, and pneumonia. Laboratory abnormalities included elevated aPTT and serum creatinine; these were expected as patients had received dabigatran and renal dysfunction was common in this population. Elevated liver function tests were seen in 3 patients (cholelithiasis and cholecystectomy (1), renal and hepatic failure (1), sepsis with multiorgan failure (1)).

Immunogenicity data were available in 47 patients. Two patients had baseline, nonspecific anti-drug antibodies. One patient had a treatment-emergent ADA of mixed specificity.

9. Advisory Committee Meeting

This BLA was not presented at an advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class.

10. Pediatrics

The Applicant received Orphan drug designation for idarucizumab for this indication. Therefore, the Applicant is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

Proprietary name review:
The proposed proprietary name, Praxbind, was reviewed by DMEPA/OMEPRM/OSE. The proposed name was acceptable from a promotional and safety perspective.

OSE/OPE Division of Epidemiology I consultation:

- OSE/OPE provided comments and recommendations for a postmarketing clinical safety study for idarucizumab. The review noted that "*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 adverse drug reactions, postmarketing…DEPI recommends issuing a PMR for a clinical safety study to provide additional assurance that serious adverse drug reactions, such as serious hypersensitivity reactions, do not occur commonly with idarucizumab. A target sample size of 1000 exposed patients could provide assurance that serious adverse drug reactions not observed during the study are unlikely to occur in more than three per thousand patients treated with idarucizumab*". The second recommendation is for "*the sponsor [to] 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).*"

  Regarding the first recommendation, Dr. Kaminskas in his review does not see any utility of expanding the presently ongoing study to 1000 patients: "*First, absence of a hypersensitivity reaction will not result in a labeling claim, whether it is based on 123 patients or on 1000 patients. It would be extraordinary for a one-time injection, without prior sensitization, to cause a hypersensitivity reaction. Second, the Division has approved many monoclonal antibodies of various types that cause a high incidence of hypersensitivity reactions and require premedication to alleviate these reactions. Hypersensitivity*

reactions are not a contra-indication to use, they only require appropriate care in administering the drugs. Third, the Division is not familiar with a requirement to assess the probability of a hypersensitivity reaction in approval of drugs or biologics, if none are noted in 123 patients and 283 normal human volunteers. With regard to serious adverse drug reactions, they are impossible to attribute in trauma settings or other emergency situations. A perusal of narratives submitted in the BLA is instructive but causal relationships cannot be drawn." I agree with the Division/Dr. Kaminskas regarding their rationale for not issuing this PMR.

Regarding the second recommendation, Dr. Kaminskas states—*"a review of deaths reported in Study 1321.3 does not suggest reversal of anticoagulation as causal in any of them. A comparison of total numbers of deaths between the on-going trial and the "historical" trials would suffer from multiple deficiencies, including that of being grossly underpowered. In the so-called "historical" dabigatran trials the patients who had a major hemorrhage or required emergency surgery would have been withdrawn from the study. Criteria for inclusion in the on-going study were criteria for exclusion in the "historical" studies. The Division fails to see the utility of such a study, which certainly would not result in labeling."* I also agree with the Division/Dr. Kaminskas regarding this concern.

Risk Evaluation ad Mitigation Strategy (REMS) Review:

OMEPRM/OSE concluded as follows: "At this time, based on the risks of 1) thrombotic events (of a patient's underlying disease) when dabigatran therapy is discontinued and idarucizumab anticoagulant reversal is initiated and 2) potential hypersensitivity reactions to idarucizumab, the DRISK and the DHP concurred that a REMS is not needed to ensure that the benefits of idrucizumab outweigh the risks for this therapeutic biologic formulation. The DHP and the DRISK agreed that prescribers are informed on the serious risks associated with discontinuation of dabigatran treatment when initiating an antidote for reversal of the anticoagulant effect of dabigatran. The DHP and DRISK concurred that the reported adverse events/reactions do not appear to be causally attributed to idarucizumab."

Office of Study Integrity and Surveillance Review:

- The bioanalytical portions of healthy volunteer studies were inspected regarding method validation for anti-dug antibodies. Non-reproducibility of confirmatory assay was detected. The recommendation was made that the analytical data for ADA in these studies be accepted, if the non-reproducibility and specificity of the confirmatory assay did not impact the study outcome.
- Inspection of the clinical portions of healthy volunteer studies revealed that repeat analysis of coagulation tests in 501 samples for 22 subjects was required because the pre-dose clotting time was higher than the acceptable upper limit of normal. No significant issues were observed and no Form 483 was issued. A recommendation was made to accept the clinical data.
- On-site inspections of two clinical sites were not performed, because these sites had been recently inspected. One site received a No Action Indicated outcome, the other had an outcome of Voluntary Action Indicated. The reviewer recommended accepting data without an on-site inspection.

Office of Prescription Drug Marketing and Promotion (OPDP):

OPDP has reviewed and provided comments on the Applicant's proposed promotional materials for product launch.

There are no other unresolved relevant regulatory issues.

12. Labeling

The entire review team and reviewers from DMEPA reviewed prescribing information, container labels, (b) (4) . All issues were resolved.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action recommended: *Accelerated Approval*.

- Risk Benefit Assessment: I concur with the detailed analysis of risk/benefit by the clinical reviewer and Dr. Kaminskas: *"Patients treated with dabigatran are at increased risk for bleeding, as are patients treated with all other anticoagulants. Idarucizimab reverses the anticoagulant effect of dabigatran; this reversal is an important clinical benefit to patients who require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. Although the safety database is limited, there have been no adverse reactions that could be causally related to idarucizumab. Effective reversal of anticoagulant effect of dabigatran in absence of serious safety concerns supports the conclusion that benefit greatly outweighs the risks."*

- Recommendation for Postmarketing Risk Management Activities
  None.

- Recommendation for other Postmarketing Study Commitments
  See action letter.

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/s/

TAMY E KIM
10/16/2015

RICHARD PAZDUR
10/16/2015