



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

**Andexanet alfa, Factor Xa Inhibitor antidote (BLA 125586/0)
Pharmacovigilance Plan Review Memorandum**

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Office of Blood Research and Review (OBRR)

Subject: Pharmacovigilance Plan Review Memorandum

Applicant: Portola Pharmaceuticals, Inc.

Product: Andexanet, Factor Xa Inhibitor Antidote

Proprietary Name: Andexxa

Established/Proper Name: Recombinant modified human factor X

BLA Submission: Original BLA 125586/0
[IND 15089]

Proposed Indication: Andexanet alfa is indicated for patients treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations such as life-threatening or uncontrolled bleeding (b) (4)
[REDACTED]

Action Due Date: August 17, 2016 (priority review)

1. INTRODUCTION

1.1 Objectives/Scope

This memorandum is in response to a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan submitted by Portola Pharmaceuticals, Inc. for the original BLA 125586/0 seeking initial licensure for the product Andexanet alfa (proposed trade name: Andexxa), a recombinant modified human factor Xa (fXa), developed as a specific reversal agent for the anticoagulant effects of fXa inhibitors. The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies, should the product be approved.

1.2 Product Description

Andexxa was developed as a specific reversal agent for anticoagulant effects of both direct and indirect fXa inhibitors. Andexxa is a recombinant human factor Xa (fXa), genetically modified to be catalytically inactive, while retaining the ability to bind fXa inhibitors with high affinity. Once bound, the fXa inhibitors are unable to bind to and inhibit endogenous fXa, thus allowing for restoration of normal hemostasis. Clinical and non-clinical data suggest that the predominant mechanisms of action are sequestration of the fXa anticoagulant, decrease in the free fraction of the inhibitor and reversal of the anti-fXa activity allowing a definitive hemostatic plug to form and stabilize during the first hour after dosing.¹

The proposed indication is described as follows:

Andexanet alfa is indicated for patients treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations such as life-threatening or uncontrolled bleeding (b) (4).

1.3 Background

Oral (direct) fXa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, betrixaban) represent a new class of anticoagulants that are rapidly increasing in use and replacing older drugs. Parenteral (indirect) anti-thrombin III dependent fXa inhibitors such as (b) (4) and low molecular weight heparins (enoxaparin) have been in use for years. Both direct and indirect fXa inhibitors may be associated with increased bleeding events, which may be life-threatening. Reversal of anticoagulation while on fXa-inhibitors may be achieved by fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). In clinical trials of patients with atrial fibrillation receiving fXa inhibitors, major bleeding occurred at an annualized rate of 2.1 to 3.5%. Rates of major bleeding episodes for patients taking direct fXa inhibitors have been reported from 1.0% to as high as 3.6%.² Based on the published incidence of major bleeding in multiple Phase 3 studies with fXa inhibitors and their projected uptake, it is estimated that > 100,000 patients treated with these agents will suffer a serious life-threatening bleed annually in the US.³

¹ 1.11.3 Clinical Information Amendment

² BLA 125586, section 1.16.1, Risk Management, p.7

³ BLA 125586, section 1.16.1, Risk Management, p.21

Anticoagulation-related major bleeding is associated with an increased risk of death as well as increased thrombotic events, independent of the class of anticoagulant used.⁴ Patients who receive fXa inhibitors may also be at increased risk of bleeding if emergency surgery is required.

1.4 Regulatory History

- August 14, 2013: Type B meeting between sponsor and CBER – The sponsor was advised that based on the proposed clinical development plan, data obtained using surrogate markers in healthy volunteers may support an accelerated approval pathway, if the proposed surrogates can be shown to reasonably predict clinical outcomes, and would need to be validated in a phase 4 trial, and that preliminary data in bleeding patients would be required for approval.⁵
- November 22, 2013: Andexxa was granted Breakthrough Therapy designation
- February 23, 2015: Andexxa was granted Orphan designation.
- November 6, 2015: Portola submitted original BLA 125586/0 as a rolling submission. The Risk Management Plan (module 1.16) was submitted in an amendment and received on February 4, 2016.⁶

2. MATERIALS REVIEWED

Document Reviewed	Source
1.16 Risk Evaluation and Mitigation Strategy 5.3.5.3 Integrated Summary of Safety 2.5 Clinical Overview 2.74 Summary of Clinical Safety 1.14 Proposed labeling and proposed Package Insert	BLA 125586/0
Input from BLA review team	Review team discussions with CBER staff; draft clinical review memo

Pertinent published literature was also reviewed and is referenced in this memo.

There are no post-licensure data for review, as the product has not been marketed in any country.

3. CLINICAL SAFETY DATABASE

DE defers to OBRR clinical review for full review of premarket clinical safety database. The premarket clinical safety database consists of:

- Completed studies 14-503 and 14-504 in healthy volunteers; N = 148 subjects
 - Study 14-503 included 68 subjects who received apixaban
 - Study 14-504 included 80 subjects who received rivaroxaban
- Ongoing study 14-505 (ANNEXA 4) to treat bleeding patients; N = 57 subjects to date

⁴ Giugliano RP, R.C., Braunwald E, et al., *Edoxaban versus Warfarin in Patients with Atrial Fibrillation*. New England Journal of Medicine, 2013(369): p. 2093-104.

⁵ FDA EOP2 Meeting Summary 9/13/2013

⁶ BLA 125586, section 1.16.1, Risk Management

Clinical Trials 14-503 and 14-504 provided the primary evidence to support safety and efficacy for Andexxa. Data from the ongoing confirmatory study 14-505 were submitted as supportive evidence of safety and effectiveness.

3.1 Studies 14-503 and 14-504 (completed studies in healthy volunteers)

Study 14-503

Title of Study: A Phase 3 Randomized, Double-blind, Placebo-controlled Study in Older Subjects to Assess Safety and Reversal of Apixaban Anticoagulation with Intravenously Administered Andexanet Alfa [Andexxa]

Objectives: To compare Andexxa and placebo with respect to reversal of apixaban (Eliquis) anticoagulation as measured by anti-fXa activity, both after a bolus and after a bolus followed by a continuous infusion

Study population: 68 healthy volunteers (50-75 years of age) who received apixaban

Safety follow-up: Subjects were followed for safety through approximately Day 43.

Study 14-504

Title of Study: A Phase 3 Randomized, Double-blind, Placebo-controlled Study in Older Subjects to Assess Safety and the Reversal of Rivaroxaban Anticoagulation with Intravenously Administered Andexanet Alfa

Objectives: To compare reversal of rivaroxaban anticoagulation between andexanet alfa and placebo as measured by anti-Factor Xa (fXa) activity, both after bolus and after bolus followed by continuous infusion.

Study population: 80 healthy volunteers (50-75 years of age) who received rivaroxaban

Safety Results for studies 14-503 and 14-504: Please see OBRR clinical memo for full review of premarket clinical safety database. The most common treatment emergent AEs (TEAEs) related to study drug in the pooled Andexxa and pooled placebo analysis datasets were infusion-related reaction (17.5% vs. 6.4%), and dizziness postural (1.3% vs. 3.2%, respectively). There were no thrombotic events noted in healthy volunteers in studies 14-503 and 14-504. There were no deaths. Low levels of non-neutralizing antibodies were observed in study 14-504; but no cross-reacting antibodies against fX or fXa were confirmed.

Reviewer comments: The study population of studies 14-503 and 14-504 comprises healthy volunteers, to measure fXa activity, which is a surrogate endpoint to measure reversal of anticoagulation by fXa inhibitors. Clinical trials in healthy volunteers will not evaluate whether clinical outcomes are improved for the indicated population of bleeding patients. There is limited data from the ongoing study ANNEXA 4 to treat bleeding patients. As noted by the clinical reviewer, “Generalizability of the healthy volunteer studies to the target population is limited because renally impaired patients were excluded, as were patients with an increased baseline risk of thrombosis.” Furthermore, studies 14-503 and 14-504 did not include evaluation of reversal of anticoagulation by edoxaban and enoxaparin.

3.2 Study 14-505/ANNEXA 4 (ongoing phase 3b/4 study in bleeding patients)

Title of Study: Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding

Objectives: The objective is to evaluate the hemostatic efficacy of Andexxa in fXa-inhibitor treated patients with acute major bleeding, and to demonstrate the decrease in anti-fXa activity following Andexxa

Safety Objectives:

- To evaluate the overall safety of andexanet, including adjudicated thromboembolic events and antibodies to fX, FXa, and andexanet
- To evaluate the 45-day all-cause mortality

Sample Size: A sample size of 162 efficacy evaluable patients will provide 80% power for a two-sided 95% CI that is completely above 50% for the primary efficacy variable of effective hemostasis. This is based on an anticipated response rate of 61%. It is estimated that approximately 30% of the safety population will have anti-fXa activity < 75 ng/mL and will therefore not be included in the efficacy analysis. It also is estimated that up to 5% of patients will be unevaluable for other reasons. Therefore, it is anticipated that up to 250 patients may have to be treated to achieve the requisite number of efficacy evaluable participants.

Data on 57 subjects has been submitted thus far, as per the 180-day safety update (BLA 125586 Day 180 amendment; submitted June 14, 2016).

Safety Results: Please see OBRR clinical memo for full review of premarket clinical safety database and case narratives.

Table 1: Subject Disposition – Ongoing 3b/4 Study in Bleeding Patients (14-505)

Factor Xa Inhibitor N = Patients (n%)				Total Receiving Andexanet
Patients Enrolled	Rivaroxaban 24 (42.1)	Apixaban 27 (47.4)	Enoxaparin 6 (10.5)	All Patients 57 (100)
TEAEs	13	16	1	30 (52.6)
Deaths	3	5	0	8 (14.0)
SAEs	7	10	1	18 (31.6)
Discontinued Study Drug	0	0	0	0

Of the 57 patients in the safety population, 30 had at least one TEAE, 18 had at least one SAE, 8 patients died, and no patients discontinued the study drug.⁷

Deaths: There were a total of 8 deaths, including two that were considered related to Andexxa by the FDA reviewers.

Table 2: Deaths in Ongoing Phase 3b/4 Study (14-505)

Patient ID	Cause of Death	Study Day	Relatedness as per DE review
Rivaroxaban			
(b) (6)	Intracerebral hemorrhage	1	Unrelated
	Ischemic stroke	2	<i>Probably related</i>
	Subdural empyema	7	Unrelated
	Acute MI/Unspecified accident	8	<i>Probably related</i>
Apixaban			
(b) (6)	Pneumonia, respiratory failure	21	Unrelated

⁷ 2.7.4 Summary of Clinical Safety

(b) (6)	Cardiogenic shock	21	Unrelated
	Cardiopulmonary arrest	18	Unrelated
	Cardiogenic shock	17	Unrelated

Case narratives for selected death reports, assessed as related to study drug:

- (b) (6): 95-year-old patient with multiple comorbidities (prior history of stroke, TIA, atrial fibrillation, congestive heart failure, hypertension, hyperlipidemia, diabetes) developed aphasia and hemiplegia 6.5 hours after the end of Andexxa infusion with MRI evidence of stroke.
- (b) (6): The case of the unspecified accident occurred in an 84-year-old patient who suffered an acute myocardial infarction shortly after receiving Andexxa. She had multiple risk factors including a prior history of MI, atrial fibrillation, renal failure and COPD, PE, CHF, hypertension, colon cancer, and prior tobacco use. She was discharged to a nursing home where she had an “unspecified accident” and died. The cause and nature of the accident is unknown.

Non-Fatal Serious Adverse Events (SAEs): There were 37 non-fatal SAEs reported in 18 subjects. All were considered unrelated by FDA reviewers and the study investigators.

Adverse Event of Special Interest: Thromboembolic events (TEEs):

- Nine subjects in the confirmatory study had 16 AEs that were considered “potentially thrombotic in nature.” The events occurred 2 to 30 days after dosing in subjects with medical histories of recent DVT alone (2 patients), DVT and atrial fibrillation (1 patient), or atrial fibrillation alone (4 patients). None of the subjects were re-anticoagulated after treatment with Andexxa. Three of the thrombotic events (ischemic stroke in subject (b) (6), acute MI in subject (b) (6), and multiple DVTs in subject (b) (6)) were all considered related to Andexxa by the OBRR clinical reviewer and the DE reviewer. The case of multiple DVTs (Subject (b) (6)) did not lead to death.
- There remain unresolved safety concerns about the procoagulant properties of Andexxa. Andexxa’s impact on mechanisms related to the tissue factor pathway inhibitor (TFPI) has not been fully investigated.
- Portola has not developed assays to detect anti-drug antibodies (ADAs) that may neutralize endogenous coagulation factors X and Xa. Thus there is missing information on the risk of development of neutralizing antibodies (inhibitors).

Reviewer comment: In this population of patients with an increased baseline risk of thrombosis, reversal of anticoagulation carries an inherent risk for thromboembolic events. Reversing fXa inhibitor therapy exposes patients to thrombotic risk of the underlying disease. To reduce this risk, resumption of anticoagulation therapy should be considered as soon as the patient is stabilized and anticoagulation is medically appropriate. As noted by the clinical reviewer, “Thrombotic events were an expected AE as Andexxa has some procoagulant properties and because effectively reversing anticoagulation in patients who have an increased baseline risk for thrombosis increases the likelihood that such an event will occur on antithrombotic therapy patients.” The study design does not include a comparator control arm, which limits assessment

of TEEs in a limited data set of 57 subjects. The clinical reviewer concludes that “The risk of thrombosis cannot be adequately assessed with this safety database because of the limited data provided in the submission and a lack of an adequate control group to understand baseline rates of thrombosis in this population.” In addition, there is missing information on characterization of its procoagulant properties, immunogenicity, and potential for development of inhibitors.

4. Literature Review

1. The new oral anticoagulants: Reasonable alternatives to warfarin.

Roca B, Roca M. *Cleve Clin J Med.* 2015 Dec;82(12):847-54.

Compared with vitamin K antagonists, these are more convenient, do not require laboratory monitoring, have limited drug and food interactions, and have fixed dosages suitable for most patients. But the shortcomings of these agents can jeopardize their efficacy and increase the risk of bleeding.

2. Antidote reverses anticoagulant effects of factor Xa inhibitors in minutes, studies show.

Mayor S. *BMJ.* 2015 Nov 12;351:h6086

Despite the current limitations in knowledge, andexanet represents a giant step forward in our ability to control anticoagulation therapy.

3. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity.

Siegal DM, Curnette JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA.

N Engl J Med. 2015 Dec 17;373 (25);2413-24.

Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects.

4. Antidote for Factor Xa Anticoagulants.

Connors JM. *N Engl J Med.* 2015 Dec 17;373(25):2471-2.

Andexanet was associated with rapid and significant reductions in anti-factor Xa activity. Despite current limitations in knowledge, andexanet represents a giant step forward in our ability to control anticoagulation therapy.

The above comments represent the authors’ conclusions. Review of the literature did not reveal new safety concerns for this product.

5. PHARMACOVIGILANCE PLAN REVIEW⁸

Safety concerns as per Portola’s proposed pharmacovigilance plan (PVP) (received 2/4/16, BLA 125586/0.5) are described in the table below. The PVP includes the manufacturer’s assessment of identified and potential risks and missing information based on pre-licensure clinical trials, published literature, and known product-class effects.

⁸ Section 1.16.1.2.1 Pharmacovigilance Plan

Table 3: Safety Concerns and Proposed Pharmacovigilance Activities

Safety Concern	Planned Action(s)
Important Identified Risks: Mild and moderate infusion reactions	Mild to moderate infusion reactions have not been reported in the acutely bleeding population; only in healthy volunteers. There are no planned pharmacovigilance actions for infusion reactions.
Important Potential Risks: Antibody formation	There are no planned pharmacovigilance actions for this potential risk. No human subject has ever developed antibodies that would lessen the pharmacodynamics effect of andexanet alfa (neutralizing antibodies). To date there still have been no confirmed antibodies against either fX or fXa.
Important Missing Information: 1) No information in pregnant females for effects on the fetus. 2) No information in lactating females for effects on the infant. 3) No information for effects in the pediatric population.	The label indicates that there is no information on use in children, pregnancy, or lactation and that use is not recommended in these populations.

Routine pharmacovigilance includes adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years (annual thereafter). Routine pharmacovigilance also includes continuous monitoring of the safety profile including signal detection, issue evaluation, updating labeling as necessary, and liaison with regulatory authorities.

6. Integrated Risk Assessment

DE has reviewed Portola’s proposed pharmacovigilance plan (received 2/4/16, BLA 125586/0.5) which proposes routine pharmacovigilance for Andexxa, should the product be approved.

Portola states that, “The safety specification for andexanet alfa [Andexxa] indicates that the important identified and potential risks, including missing information, for the product are few and can be safely and effectively managed by routine pharmacovigilance practices.” However, at this time, the clinical safety database is limited and there remain unresolved safety concerns.

The sponsor’s proposed pharmacovigilance plan fails to account for the following:

- Thromboembolic events emerged as an important identified risk from safety data received in the 180-day safety update. Because of the small sample size, and multiple comorbidities of the patients, no subgroups were identified to have been at increased risk.
- Absence of a validated assay to measure antibody formation (important potential risk) and development of neutralizing antibodies. Anti-drug antibodies may also potentially bind to endogenous fXa. Andexxa was tested in clinical studies as a single bolus with or without infusion and has not been tested across repeated exposure.
- Missing information: study population did not include subjects treated with edoxaban and enoxaparin and there is no safety data in this population.
- Studies 14-503 and 14-504 in healthy volunteers to measure surrogate endpoint (fXa activity) did not evaluate clinical outcomes in the indicated population of bleeding patients.
- The confirmatory study in bleeding patients (study 14-505/ANNEXA 4) is currently ongoing; there is limited data from 57 subjects.

- There remain unresolved clinical and CMC issues, including the proposed dosing regimen, Andexxa's impact on mechanisms of action related to the tissue factor pathway inhibitor (TFPI), study design of confirmatory study in bleeding patients, including recommendations for a comparator arm ("usual care cohort").

Final determination of the benefit/risk profile of Andexxa is pending the final clinical, statistical, CMC and product reviews.

7. DE Recommendations

There is limited available safety data in bleeding patients, insufficient data in reversal of anticoagulation by edoxaban and enoxaparin, and unresolved safety concerns related to thromboembolic events, characterization of procoagulant properties and immunogenicity of this product. FDA is engaged in ongoing discussions with the sponsor regarding the study design for a confirmatory clinical study to collect additional efficacy and safety data.

At this time, OBRR has determined that Andexxa cannot be granted final approval because of multiple deficiencies involving CMC and clinical review issues, and a Complete Response (CR) Letter will be issued. DE reserves comment on the proposed pharmacovigilance plan until the application is otherwise acceptable. DE will review the proposed final pharmacovigilance plan and a postmarketing study protocol when submitted in response to the CR Letter.