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

ANDEXXA (andexanet alfa)
BLA 125586
Pharmacovigilance Plan Review Memorandum

From:	Faith Barash, MD MPH Medical Officer, Pharmacovigilance Branch (PVB) Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE)
Through:	Adamma Mba-Jonas, MD Branch Chief, PVB Scott Proestel, MD Director, DE
To:	Mikhail Ovanesov, PhD Chair, BLA 125586 Review Committee Office of Blood Research and Review (OBRR)
Subject:	Pharmacovigilance Plan Review Memorandum
Applicant:	Portola Pharmaceuticals, Inc.
Proprietary Name:	ANDEXXA
Established/Proper Name:	Coagulation Factor Xa (Recombinant), inactivated
BLA Submission:	Original BLA 125586/0 - Class II resubmission [IND 15089]
Proposed Indication:	For patients treated with direct Factor Xa inhibitors, rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life threatening or uncontrolled bleeding
Action Due Date:	May 4, 2018

1. Introduction

1.1 Objectives/Scope

This memorandum is in response to a request from the Office of Tissues and Advanced Therapies (OTAT) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan submitted by Portola Pharmaceuticals, Inc. for the original BLA 125586/0. The sponsor is seeking licensure for the product 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 the 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 binding and sequestration of the fXa anticoagulant, decrease in the free fraction of the inhibitor and reversal of the anti-fXa activity allowing a hemostatic plug to form and stabilize during the first hour after dosing.[1] A second mechanism of action is a more sustained inactivation of plasma tissue factor pathway inhibitor (TFPI), an endogenous inhibitor of blood coagulation, which may contribute to the pro-coagulant activity of ANDEXXA *in vivo*.

The proposed indication is as follows:
ANDEXXA is a recombinant modified human Factor Xa (FXa) protein indicated for patients treated with a FXa inhibitor (Apixaban or Rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

1.3 Background

Oral (direct) fXa inhibitors (e.g., rivaroxaban (xarelto), apixaban (eliquis), edoxaban (savaysa), betrixaban (bevyxxa)) 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 fondaparinux (arixtra) 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

---

[1] 1.11.3 Clinical Information Amendment
[2] BLA 125586, section 1.16.1, Risk Management, p.7

bleed annually in the US.[3] 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.

This is Portola's resubmission of a marketing application in response to a complete response letter, issued on August 17, 2016. The applicant seeks approval under the Accelerated Approval pathway for reversal of anticoagulation in patients treated with rivaroxaban and apixaban for the reversal of life-threatening or uncontrolled bleeding.

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]
- During the review process, CMC and clinical data were found to be insufficient to support approval of the application.
- On August 17, 2016, Portola was issued a complete response letter due to CMC and clinical concerns.[7]
- On August 4, 2017 Portola resubmitted the application, with CMC deficiencies addressed.
- Clinical data in Study 14-505 was submitted as clinical confirmation.
- Usual Care Cohort study protocol 16-510 submitted
- Clinical data submitted classified as a major amendment, adjusting the ADD by 3 months to May 4, 2018
- Randomized Controlled Trial (RCT) protocol submitted March 16, 2018
- Teleconference discussion with Portola March 23, 2018 to discuss feasibility of accelerated approval and plans for ongoing studies (Pre- versus Post-marketing)
- April 9, 2018 Ongoing discussions about Black Box Warning for Thromboembolic Events

---

[3] BLA 125586, section 1.16.1, Risk Management, p.21
[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
[7] BLA Complete Response August 17, 2016

2.   Materials Reviewed

Document Reviewed	Source
1.16 Risk Evaluation and Mitigation Strategy 1.13.15 Summary of Safety Information 5.3.5.1 Study Reports of Controlled Clinical Studies 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 16-510 Usual Care Cohort Study Protocol 18-513 Randomized Controlled Trial Protocol	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 the OTAT clinical review for full review of the premarket clinical safety database. In the original BLA submission, the applicant reported on two completed Phase 3 studies (14-503 and 14-504) for reversal of anticoagulation following treatment with apixaban and rivaroxaban in healthy volunteers. In addition to the healthy volunteer study, data from the ongoing Phase 3b/4 study ANNEXA-4 (Study 14-505) of ANDEXXA for treatment of subjects who experienced life threatening bleeding following anticoagulation with rivaroxaban, apixaban or enoxaparin (Lovenox) were included. The efficacy endpoint to support a marketing claim was based on the surrogate endpoint of a decrease in anti-fXa activity in the healthy volunteer studies. ANNEXA-4 was designed to serve as the confirmatory study to evaluate efficacy in the target (bleeding) population. 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 patient (N = 185 evaluable patients)

Clinical Trials 14-503 and 14-504 provided the primary evidence in support of safety for ANDEXXA.
At this writing, it is unknown whether this submission will be approved under the accelerated approval process, be transitioned to traditional approval process, conduct randomized controlled trial as a pre- or post-marketing study, or be given a non-approval complete response.

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 (Xarelto) 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 OTAT 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 is comprised of healthy volunteers, to measure fXa activity, which is the sponsor's proposed 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. As noted by the clinical reviewer, "Generalizability of the healthy volunteer studies to the target population is limited because patients with renal impairment 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 (ANNEXA-4)

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
Indication studied: Reversal of anticoagulation when presenting with acute major bleeding

following treatment with one of the following: apixaban, rivaroxaban, edoxaban, or enoxaparin

Study population: Patients presenting for care at hospitals or EDs with acute major bleeding, who have received one of the following FXa inhibitors within 18 hours of presentation: apixaban, rivaroxaban, edoxaban, or enoxaparin; the definition of major bleeding is based on the International Society of Thrombosis and Haemostasis (ISTH) definition. 185 subjects enrolled as of data lock point of October 17, 2017; 250 planned.

Safety Objectives:
- To evaluate the overall safety of ANDEXXA, including adjudicated thrombotic events (TEs) and antibodies to fX, FXa, and ANDEXXA
- To evaluate the 30-day all-cause mortality

Methodology: Since there is no available standard of care for reversal of anticoagulation from FXa inhibitor drugs, randomized active comparator trials were not considered possible. Additionally, use of a placebo control was not considered ethical due to the risk of serious morbidity and mortality from uncontrolled acute major bleeding. Enrolled patients received ANDEXXA as an IV bolus administered over 15-30 minutes, followed by a continuous infusion administered over approximately 120 minutes. The start of the ANDEXXA bolus began within 18 hours of the last dose of the FXa inhibitor. If the timing of the last dose was unknown, the infusion began as soon as possible, but no later than 3 hours after signing consent. Patients received one of two dosing regimens depending on which FXa inhibitor they received and the dose and time of the most recent dose. The two possible dosing regimens were:
- Bolus of 400 mg at target rate of 30 mg/min followed by continuous infusion of 480 mg at 4 mg/min for 120 minutes
- Bolus of 800 mg at target rate of 30 mg/min followed by continuous infusion of 960 mg at 8 mg/min for 120 minutes

Per the study protocol, patients were to be resumed on anticoagulation as soon as medically feasible.

Sample Size: Per the sponsor, a sample size of 250 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 fail to demonstrate baseline levels of anticoagulation necessary to make evident the efficacy of the product 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.

Safety Results: Subjects who received one dose of ANDEXXA were considered evaluable for safety. The sponsor did not provide data on non-serious AEs in the complete safety population. However, this data was available for the 101 patients in the initial submission. Of these 101 patients, 52 experienced a total of 122 AEs. Overall, the most frequently reported AEs in this population (occurring in more than 2% of patients) were cardiac arrest, sepsis, headache, seizure,

pulmonary embolism, and respiratory failure (3 patients each), and pneumonia, urinary tract infection, and deep vein thrombosis (4 patients each).

Information on SAEs was provided for the complete safety population (N=185).
Overall, 65 (35.1%) patients in this group had at least 1 SAE and there was a total of 117 SAEs.
Five SAEs occurred in > 2% of the safety population; these included pneumonia (7 patients), pulmonary embolism and respiratory failure (5 patients each), and deep vein thrombosis and sepsis (4 patients each).

Of note, no infusion reactions were seen in the safety population.

The sponsor identified thrombotic events as adverse events of special interest.
Of the 185 patients in the safety population, 23 (12.4%) had a reported TE during follow up, prospectively defined as a deep vein thrombosis (DVT), MI, pulmonary embolism (PE), cerebrovascular accident (CVA), or transient ischemic attack. The median time to first event was 11 days. Information about resumption of anticoagulation was available for all patients who had experienced a TE. There was an imbalance in the incidence of TE in patients who had resumed anticoagulation within 30 days of treatment (18/169, 10.7%), vs. patients who had not resumed anticoagulation (5/16, 31%).

Of the 185 subjects in the safety population, there were 23 deaths reported. Deaths are summarized in the table below.

ANNEXA-4 (14-505): Summary of Deaths

	DSUR Safety Population (N=185)
Number of Deaths	23 (12.4%)
All Non-cardiovascular	15 (8.1%)
• Respiratory Failure	3 (1.6%)
• Accident or Trauma	1 (0.5%)
• Bleeding	2 (1.1%)
• Infection/Sepsis	2 (1.1%)
• Other Non-vascular Cause	7 (3.8%)
All Cardiovascular	8 (4.3%)
• Sudden Cardiac Death (including unwitnessed)	3 (1.6%)
• Cardiac Mechanical/Pump Failure	1 (0.5%)
• Stroke	1 (0.5%)
• Other Cardiovascular Cause	3 (1.6%)
Death Preceded by	
• Myocardial Infarction	0
• Stroke	2 (1.1%)

• Pulmonary Embolism	1 (0.5%)
• Deep Vein Thrombosis	1 (0.5%)

Source: DSUR Figure 2, Appendix 6

The majority of deaths (91.3%; 21/23) occurred greater than 72 hours after ANDEXXA administration, with the exception of a patient who died of cardiac arrest one day after treatment and a second patient who died of intracranial hematoma three days after treatment. Of note, ANDEXXA has a mean terminal half-life of approximately 5 to 7 hours and an effective (biological) half-life of approximately 1 hour when studied in healthy volunteers. The half-life of factor X (the inactive form of Factor Xa) is 40-45 hours. The half-lives of Apixaban and Rivaroxaban are 12 hours and 5-9 hours, respectively.

4. Literature Review

The comments below represent conclusions of the authors of the papers.

1. <u>The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1626 patients.</u>
Prandoni P, Noventa F, Ghirarduzzi A, Pento V, Bernardi E, Presavento R et al.
Haemotologica 2007;92:199-205
After discontinuing anticoagulation the rate of recurrent VTE increases steadily over time, approaching 40% among all patients after 10 years. The rate of VTE in the first year was 11%.

2. <u>Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients</u>.
Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM.
NEJM. 2011 Nov 13; NEJM.ORG.
In medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin.

3. <u>The new oral anticoagulants: Reasonable alternatives to warfarin</u>.
Roca B, Roca M. Cleve Clin J Med. 2015 Dec;82(12):847-54.
Compared with vitamin K antagonists, factor Xa inhibitors are more convenient, do not require laboratory monitoring, and have limited drug and food interactions. Fixed dosages are suitable for most patients. These agents can increase the risk of bleeding.

4. <u>Antidote reverses anticoagulant effects of factor Xa inhibitors in minutes, studies show</u>.
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 in the opinion of the author.

5. <u>Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity.</u>
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.

6. 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 step forward in our ability to control anticoagulation therapy.

7. Long-term risk of venous thrombosis after stopping anticoagulants for a first unprovoked event: A multi-national cohort
Rodger M, Scarvelis D, Kahn S, Wells P, Anderson D, Chagnon I, Le Gal G, Gandara E et al.
Thrombosis Research. 2016 Mar 23; 143:152-158
The long-term risk of recurrent VTE in patients after unprovoked VTE was approximately 30% at 8 years.

8. Reversal of direct oral anticoagulants.
Almegren M.
Vasc Heath Risk Manag. 2017 Jul 19; 13:287-292.
Andexanet alfa is a specific antidote for direct and indirect factor Xa inhibitors. It has the potential to reverse the anticoagulant effects that specifically target activated factor X. As of the time of publication, andexanet alfa was under evaluation in ongoing Phase IIIb/IV studies. Preliminary results showed excellent efficacy, but in one study, 18% experienced thrombotic events.

9. Andexanet alfa for the reversal of anticoagulant activity in patients treated with direct and indirect factor Xa inhibitors.
Nafee T, Aslam A, Chi G, Pahlavani S, Nimri D, Kuchkuntla AR, Talib U et al.
Expert Rev Cardiovasc Ther. 2017 Apr; 15(4):237-245.
Preliminary results of phase 3b/4 trials demonstrate favorable efficacy and safety profile in patients with acute hemorrhage.

10. Reversing factor Xa inhibitors – clinical utility of andexanet alfa.
Kaatz S, Bhansali H, Gibbs J, Lavender R, Mahan CE, Paje DG.
J Blood Med. 2017 Sep 13;8: 141-149.
Andexanet alfa is a FXa decoy designed to reverse anti-FXa DOACs.

11. Management of rivaroxaban- or apixaban- associated major bleeding with prothrombin complex concentrates: a cohort study
Majeed A, Agren A, Holmstrom Mk Bruzelius M, Chaireti R, Odeberg J, Hempel EL.
Blood. 2017 Oct 12; 130(15):1706-12.
The majority of patients treated with PCCs achieved effective bleeding control, with few thromboembolic events. The rate of thromboembolism observed in this study was low, at 2.4%, but efficacy was only 69.1%.

12. <u>Stopping anticoagulation therapy after an unprovoked venous thromboembolism</u>.
Clive Kearon. CMAJ. August 26, 2008.
In the absence of risk factors for bleeding, guidelines strongly recommend that patients with a first episode of venous thrombosis or pulmonary embolism remain on indefinite anticoagulant therapy provided monitoring is achievable. Stopping anticoagulation carries a risk of recurrence of about 10% in the first year.

13. <u>Anticoagulation Reversal and Treatment Strategies in Major Bleeding: Update 2016</u>
Christos S, Naples R. Western Journal of Emergency Medicine. Volume XVII, no. 3:May 2016.
Review article outlining methods of anticoagulation reversal.

14. <u>Evidence Supporting Idarucizumab for the Reversal of Dabigatran</u>.
Pollack CV. Am J Medicine. Vol 129, No 11A, Nov 2016.
Most DOAC related bleeding does not require reversal. However, in the case of true surgical emergencies, idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88-90% of participants.

15. <u>Can I stop the warfarin? A review of the risks and benefits of discontinuing anticoagulation</u>.
Spiess JL. J Palliat Med. 2009 Jan;12(1):83-7.
Review of randomized trials show that risk of recurrent thromboembolism after stopping warfarin is 2%-10% annually.

16. <u>Clinical evidence for rebound hypercoagulability after discontinuing oral anticoagulants for venous thromboembolism</u>.
Cundiff DK. Medscape J Med. 2008;10(11):258.
Rebound hypercoagulability accounts for about 2% of patients with recurrent VTE in the first 2 months after discontinuing OACs.

17. <u>Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors</u>.
Connolly SJ, Milling TJ, Eikelboom JW, Gibson EM, Curnutte JT, Gold A. et al.
NEJM. 2016 Sept 22 375;12
Thrombotic events occurred in 18% of patients treated, and 15% died during follow-up. A controlled study will be required to assess whether the frequency of these events exceed the expected in patients at increased risk for thrombotic events.

18. <u>Clinical events after interruption of anticoagulation in patients with atrial fibrillation: An analysis from the ENGAGE AF-TIMI 48 trial.</u>
Cavallari I, Ruff CT, Nordio F, Deenadayalu N, Shi M, Lanz H, Rutman H et al.
Int J Cardiology. 2018 257; 102-107.
Interruption of anticoagulation was associated with a substantial risk of major cardiac and cerebrovascular events over the ensuing 30 days. Patients should be monitored closely and restarted on anticoagulation as soon as it is safe to do so.

19. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants
Purrucker JC, Haas K, Rizos T, Khan S, Wolf M, Hennerici MG, Veltkcamp R
JAMA neurology.com April 14 2016
Intracerebral hemorrhage related to NOAC use is associated with a high mortality and unfavorable outcome, and hematoma expansion is common. Large studies are needed to determine whether early administration of specific antidotes can improve the poor outcome of NOAC associated ICH.

20. Association of Prothrombin Complex Concentrate Administration and Hematoma Enlargement in Non-Vitamin K Antagonist Oral Anticoagulant-Related Intracerebral Hemorrhage
Gerner ST, Kuramatsu JB, Sembill JA, Sprugel MI, Endres M, Haeusler KG, Vajkoczy P, et al.
Ann Neurol 2018;83:186-196
PCC administration was not associated with a reduced rate of hematoma enlargement in NOAC-related ICH.

5.   Summary of Sponsor-Submitted Pharmacovigilance Plan[8]

Portola did not submit a new pharmacovigilance plan with the submitted amendment. 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 sponsor's assessment of identified and potential risks and missing information based on pre-licensure clinical trials, published literature, and known product-class effects.

Sponsor's Safety Concerns and Proposed Pharmacovigilance Activities

Safety Concern	Planned
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. Monitor with routine pharmacovigilance.
Important Potential Risks: Antibody formation	Per sponsor, as a biologic agent, ANDEXXA is considered capable of eliciting an immunogenic response in humans. No human subject has ever developed antibodies that would lessen the pharmacodynamics effect of ANDEXXA (neutralizing antibodies). To date there still have been no confirmed antibodies against either fX or fXa. Monitor with routine pharmacovigilance.

---

[8] Section 1.16.1.2.1 Pharmacovigilance Plan

Important Missing Information:	The label indicates that there is no 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.	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.

The sponsor plans to complete study 14-505 by continuing to enroll subjects until the goal of 250 patients has been achieved. Additionally, the sponsor is planning two post marketing studies (study protocols 16-510 and 18-513), which are described below:

Study 16-510 Usual Care Cohort
Title of Study: A Prospective Cohort study of Patients receiving a Factor Xa Inhibitor Who have Acute Major Bleeding and Receive Usual Care (Usual Care Cohort)
Objectives:
The primary objective of this study is to serve as a control to the interventional study ANNEXA-4 (14-505) which is intended to compare the hemostatic efficacy of ANDEXXA to usual care using other treatments than ANDEXXA. The UCC study is a single arm study of eligible subjects who receive usual care for treatment of bleeding, primarily ICH, in the context of use of apixaban, rivaroxaban, endoxaban or enoxaparin. Efficacy assessment is planned at 5 and 16 hours after the subject begins treatment, following baseline blood draw. Study safety endpoints are similar to the ANNEXA- 4 study protocol, and include occurrence of thrombotic events, 30-day all-cause mortality and adverse events.
Study Size: 162 subjects, of which at least 110 will have ICH bleeds.

Study 18-513 Randomized Controlled Trial
Title of Study: A Phase 4 Randomized Clinical Trial of ANDEXXA® In Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor XA Inhibitor
Efficacy Objectives:
To evaluate the effect of ANDEXXA versus usual care on the rate of effective hemostasis, and to evaluate the effect of ANDEXXA versus usual care on the change from baseline in anti-fXa activity
Safety Objectives:

- To evaluate the occurrence of thrombotic events at 30 days

- To evaluate in-hospital and 30-day mortality (all-cause, cardiovascular and bleeding)

- To evaluate the length of initial hospitalization for primary bleeding event

- To evaluate the rate of re-hospitalization

- To evaluate adverse events, vital signs and clinical laboratory measurements

- To evaluate the immunogenicity of ANDEXXA

Study Design:
This is a multicenter, prospective, randomized clinical trial designed to evaluate the effect of ANDEXXA on the rate of effective hemostasis compared to usual care in patients presenting with acute intracranial bleeding, who have recently received an oral FXa inhibitor. To avoid bias, the independent Endpoint Adjudication Committee (EAC) will be blinded to study treatment assignment. For safety purposes, treatment allocation will be unblinded to local site personnel, as the effects of concomitant use of ANDEXXA and other agents for anticoagulant reversal are not known.

Following obtaining informed consent, patients will be randomized to receive either ANDEXXA or usual care. The primary efficacy endpoint will be adjudicated based on data collected through 12 hours after randomization. The blinded, independent EAC will adjudicate efficacy, as well as all deaths and potential thrombotic events. All potential thrombotic events will be summarized descriptively, including whether the patients were re-anticoagulated prior to the event.

All AEs, including SAEs, will be followed through day 30 post-treatment.

Study Size: 420 patients are planned to be enrolled

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." The proposed plan identified infusion reaction and antibody formation as safety issues associated with the product, and proposed routine pharmacovigilance to monitor those risks. This strategy is adequate for these risks. Of note, with regards to antibody formation, the sponsor states, "No human subject has ever developed antibodies that would lessen the pharmacodynamics effect of ANDEXXA." This statement implies that no patients who have received ANDEXXA have ever generated, even temporarily, antibodies to the product, which is an unprovable statement based on the testing that was done during the clinical trials. Removal of this statement would improve the validity of this portion of the plan.

The clinical data demonstrate a reasonable likelihood of an elevated risk of thrombotic events with the use of ANDEXXA. As previously noted, occurrence of TE in the studied population may be partially due to inherent risk in these patients associated with their underlying disease, and patients are at increased risk of thromboembolism by virtue of discontinuing the anticoagulant. The thrombotic rate seen in Study 14-505 is higher (12.4%) than the rates seen in historical data published by Kearon (5% in first year in patients with reversible risk factors), and by Rodger (5% annualized risk). However, other estimates of the baseline rate of recurrent

thromboembolism after discontinuing anticoagulation are in the range of 10 - 11%[9] per year. The variation in published estimates of the rate of thromboembolism after discontinuation of anticoagulation makes it difficult to assess the true degree of increased risk associated with ANDEXXA, and in the setting of the need for urgent reversal, a slightly increased risk of TE may be acceptable. However, it is important to note that the clinical trial data seems to suggest that any risk may be further increased in patients who were not restarted on anticoagulation within 30 days of exposure to ANDEXXA.

The risk mitigation proposed by the sponsor for this safety issue includes labeling, which identifies "Thromboembolic Risk" in Section 5.1 "Warnings and Precautions." Additionally, the following is included on the first page the label under "Highlights:"

WARNINGS AND PRECAUTIONS,

THROMBOEMBOLIC EVENTS, AND ISCHEMIC EVENTS HAVE OCCURRED FOLLOWING TREATMENT WITH ANDEXXA. RESUME ANTICOAGULANT THERAPY AS SOON AS MEDICALLY APPROPRIATE FOLLOWING TREATMENT WITH ANDEXXA.

Assessment of the available data suggests that an additional boxed warning is appropriate. Per FDA guidance, boxed warnings should be used when "There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)" (FDA Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format). In the opinion of this reviewer, the noted rate of TE in the safety database for this product and the existence of a proactive clinical strategy (resumption of anticoagulation) fulfill the boxed warning requirement.

Finally, the magnitude of TE risk associated with the product is not readily apparent in the currently available data. The study design of 14-505 did not include a comparator control arm, which limits assessment of TEEs in an already limited data set of subjects. This data will be available upon completion of studies 16-510 and 18-513. Completion of these studies will be required by the product office as efficacy Post-market Requirements, and will provide critical information on incidence of TE in subjects treated with ANDEXXA. In particular, Study 18-513 will make it possible to compare this safety risk in ANDEXXA-treated patients to concomitantly enrolled control patients, optimizing the ability to assess true risk differences.

7. Conclusions
Review of the safety data indicates that there is a risk of thromboembolic events associated with the use of ANDEXXA. The magnitude of this risk has been incompletely characterized in the clinical safety database, and routine pharmacovigilance will not be sufficient to further characterize this risk. Therefore, it will be necessary to accrue additional post marketing safety data if this product is approved.

---

[9] Prandoni et al., Clive et al. Please see literature cited above.

8. Recommendations

Should ANDEXXA receive regulatory approval, Portola should be required to complete Study 14-505 with accrual of at least 250 patients, as outlined in the protocol. Study 16-510 (Usual Care Cohort), and Study 18-513, the Randomized Controlled Trial should also be conducted. The Usual Care Cohort will be considered part of the confirmatory study and the control arm for the Study 14-505. These studies will be Post-Marketing Requirements imposed by the Office of Tissues and Advanced Therapies, as required for approval by the accelerated approval pathway.

The sponsor's proposed pharmacovigilance plan is not acceptable, and should ANDEXXA gain approval, Portola will be required to submit an updated pharmacovigilance plan which acknowledges thrombotic risk as an identified risk, amends the statement describing the known information concerning the risk of antibody formation, and includes the aforementioned PMR studies. OBE agrees with OTAT on the addition of a boxed warning for the risk of thrombosis and thromboembolic events; this boxed warning should include an admonishment to clinicians to resume anticoagulation as soon as feasible.