



To Review Committee Chair

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Sponsor/Product Portola Pharmaceuticals, Inc. / FXa inhibitor antidote, ANDEXXA (Andexanet Alfa)

Subject In-support testing to measure the potency of Andexanet Alfa against direct FXa inhibitors and indirect FXa inhibitors, for licensing action of Andexanet Alfa, STN 125586

Background

A request was made by the Review Committee Chair to measure the potency of three lots of Andexanet Alfa using the Direct Inhibitor Potency Assay and the Indirect Inhibitor Potency Assay.

Summary

The potencies of three lots of Andexanet Alfa were measured in DBSQC/LACBRP of CBER using the Direct and Indirect Inhibitor Potency Assays. The assay results met all the assay validity criteria in the sponsor's SOP. The results from the three lots obtained in CBER were also within the proposed specifications for the respective assays and are comparable with the results obtained by the manufacturer.

1. Direct Inhibitor Potency Assay

Method

The potency of (b) (4) lots of Andexanet Alfa was measured at LACBRP/ DBSQC/ CBER using the Direct Inhibitor Potency Assay as described in the document TME-0850 Revision 01. This assay measures the ability of Andexanet Alfa to reverse the inhibition of FXa by binding to the FXa inhibitor, (b) (4), in a mixture containing Andexanet Alfa, FXa (b) (4). The released FXa activity is measured by (b) (4) . (b) (4) of the reference standard, assay control and test samples in the range (b) (4) were prepared in (b) (4) and measured in the assay. The mean of the (b) (4) values of reference standard, control and test samples was plotted against sample concentration ((b) (4)). Four-

parameter fit parallel line analysis was used to generate the dose-response curves. The potencies of the control and test samples were measured against the in-house reference standard provided by the manufacturer and are expressed as relative potency as percentage of the standard.

Reagents Supplied by the Sponsor

- Andexanet Alfa, In-house Reference Standard, Lot (b) (4) [REDACTED], also used as assay control, ((b) (4) [REDACTED]).
- Human Factor Xa, Lot Number (b) (4) [REDACTED]
[REDACTED]
- (b) (4) [REDACTED], FXa Inhibitor, Lot (b) (4) [REDACTED]

Results

The potency of the control and test samples were measured against the manufacturer's in-house reference standard and are reported as percentage relative potency. The results of the assay validity criteria are shown in Table 1.

Table 1: Assay Validity criteria for the Direct Potency Assay

(b) (4)

The potency results of three lots of the drug product are presented in Table 2.

Table 2: CBER/ DBSQC potency measurements for Andexanet Alfa samples using the Direct Inhibitor Potency Assay

Lot Number	Manufacturer Results	CBER Results
	Reported Value (%) ¹	% Relative Potency
	Specifications – (b) (4)	
(b) (4)	(b) (4)	97.5
(b) (4)	(b) (4)	93.8
(b) (4)	(b) (4)	102

¹ Manufacturer's results for (b) (4) are from Certificate of Analysis supplied by the Manufacturer as 125586/0.8, while manufacturer's results for (b) (4) are from stability results supplied by the manufacturer as 125586/0.57

2. Indirect Inhibitor Potency Assay

Method

The potency of (b) (4) lots of Andexanet Alfa was measured at LACBRP/ DBSQC/ CBER using the sponsor's Indirect Inhibitor Potency Assay method detailed in Document Number TME-0583 Revision 01. This assay measures the binding of Andexanet Alfa to the indirect FXa inhibitor, (b) (4), reversing the inhibition of FXa, in a mixture containing Andexanet Alfa, FXa, (b) (4). The released FXa activity is measured using an (b) (4). Measurements were made over the testing range (b) (4), covering (b) (4) dilutions of each standard, control and test samples in duplicate. The mean of the duplicate absorbance values of reference standard, control and test samples was plotted against sample concentration. Four-parameter fit parallel line analysis was used to generate the dose-response curves. The potencies of the control and test samples were measured against the in-house reference standard provided by the manufacturer and are expressed as percentage relative potency.

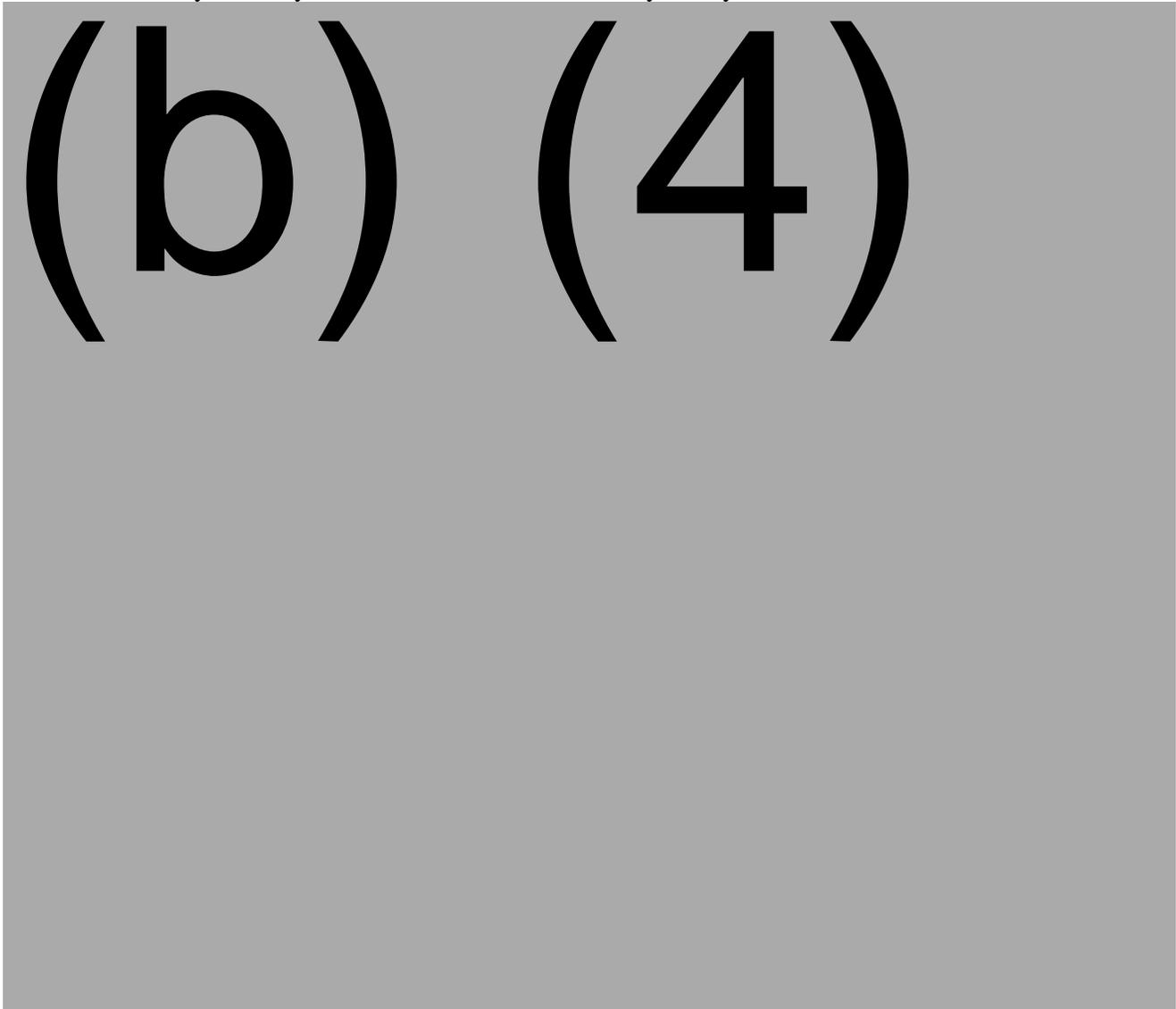
Reagents Supplied by the Sponsor

- Andexanet Alfa Reference Standard Lot # (b) (4), also used as Control, ((b) (4))
- Human FXa, Lot#(b) (4)

- (b) (4)
- (b) (4)

The potency of the control and test samples were measured against an in-house reference standard and are reported as percentage relative potency. The results of the assay validity criteria are shown in Table 3.

Table 3: Assay Validity Criteria for the Direct Potency Assay



(b) (4)

The potency of the (b) (4) lots of drug product were measured in the Indirect Inhibitor Potency assay and are presented in Table 4.

Table 4: CBER/ DBSQC potency measurements for Andexanet Alfa samples using the Indirect Inhibitor Potency assay

Lot Number	Manufacturer	CBER Results
	Reported Value (%) ¹	% Relative Potency
	Specifications – (b) (4)	
(b) (4)	(b) (4)	118
(b) (4)	(b) (4)	117
(b) (4)	(b) (4)	105

¹ Manufacturer's results are from Certificate of Analysis supplied by the Manufacturer as 125586/0.8, while manufacturer's results for (b) (4) are from stability results supplied by the manufacturer as 125586/0.57

Information Request and Review

The following IR was submitted on 6 July 2016 requesting the results. Portola responded on 7 July 2016 in Amendment 53.

Please provide your results for the Direct (b) (4), using TME-0580, and Indirect (b) (4), using TME-0583, for the following lots of drug product submitted to CBER for testing:

- (b) (4)
- (b) (4)

Review of Response: Portola stated that at the time of testing the two above-mentioned lots, the Direct and Indirect Potency assays had not yet been implemented. Hence, these lots were not tested using these methods. This is not acceptable. Hence, the following IR was submitted on 11 July 2016. The response was received on 14 July 2016 as Amendment 57.

You have stated in Amendment 53 that the Direct and Indirect Potency Assays were not implemented at the time the two lots of the drug product, (b) (4), were tested and hence you are not able to provide the requested potency data. However, we noticed in your stability data that you present Direct and Indirect potency data for Lot (b) (4) (see Table 3.2.P.8.3-5). Please provide your most recent data for your Direct and Indirect Potency measurements for Lot (b) (4), which you obtained as part of the stability test, as well as the manufacturing and/or projected expiration date for the lot. Also, please determine the potency of lot (b) (4) using the Direct and Indirect potency assays and provide us your

most recent results. If you are unable to provide this information, please send us (b) (4) additional lots of drug product for which you have test results, for example, Lots (b) (4) [REDACTED], as well as the manufacturing and/or expiration dates, along with your Direct and Indirect potency results for the (b) (4) lots you send. If you choose to send us samples, rather than submitting the potency results of lot (b) (4) [REDACTED], please also provide sufficient quantities of (b) (4) [REDACTED] to enable us to carry out this test at least (b) (4) [REDACTED] each lot.

Review of Response: In response, the sponsor provided stability data for the two lots in question using the Direct and Indirect Potency Assays. The response adequately addresses the IR. We used the results from the last data point (6 months) in this in-support testing memo.

Conclusions

The results obtained in LACBRP/DBSQC show that the potencies of Andexanet Alfa measured by the Direct Potency assay (Table 2) and Indirect Potency assay (Table 4) are within the specifications proposed for these two assays and comparable with the results obtained by the manufacturer.