

Primary Discipline Review Memo - Eloctate

Memorandum

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To: STN 125487/0

Through: Dr. William M. McCormick, Director OCBQ/DBSQC, HFM-680

Company: Biogen Idec, Inc.

Product: rFVIII-Fc (Antihemophilic Factor [Recombinant Fc Fusion Protein]); proposed proprietary name: ELOCTATETM

Subject: Discipline Review Memo for Chromogenic Potency Assay and --b(4)-----
----- the Drug Product, and other Release Tests for the
Drug Product, STN: 125487, Recombinant Factor VIII-Fc

Summary

A new BLA was submitted for recombinant coagulation factor VIII-Fc fusion protein, (STN#125487) by Biogen Idec. This document constitutes the Primary Discipline Review Memo from DBSQC for the following analytical methods and their validations, as used for lot release of the drug substance and the drug product.

Drug Substance

1. ---b(4)-----
2. ---b(4)-----

Drug Product

1. --b(4)-- and Biological Activity: Chromogenic Potency Assay
2. --b(4)-----
3. --b(4)-----
4. Residual Moisture
5. Calcium Content by --b(4)-----
6. Polysorbate 20 Assay
7. Reconstitution Time and Appearance of the Reconstituted Solution
8. --b(4)--

Review of the methods and their validations led to six Information Requests (IR). These were submitted on 7 May 2013, 18 June 2013, 24 July 2013, 26 August 2013, 29 September 2013 and 9 October 2013. The responses to the first four IRs were received on 31 May 2013, 9 July 2013, 7 August 2013, and 29 August 2013, respectively. These responses are reviewed and included in this memo. The responses to the IR dated 29 September 2013 and 9 October 2013, which relate to ---b(4)-----, Residual Moisture and Calcium Content by -b(4)----- assays, have not been received yet and review of the response to this IR will be submitted in the Addendum memo.

Conclusion: As of this Review memo, all assays for the drug product listed above, except the -b(4)-----, Residual Moisture, and Calcium Content by -b(4)----- assays, are approvable for release testing of the seven current DP strengths (250 IU/vial, 500 IU/vial, 750 IU/vial, 1000 IU/vial, 1500 IU/vial, 2000 IU/vial and 3000 IU/vial). In addition, the Chromogenic Potency Assay and the -b(4)----- - assay are also approvable for both the -b(4)-----.

Background

On March 07, 2013, Biogen Idec submitted a new BLA for recombinant coagulation factor VIII Fc (rFVIII Fc), proposed proprietary name: ELOCTATETM. rFVIII Fc is a long-acting, recombinant fusion protein comprising B-domain deleted (BDD) human factor VIII covalently linked to the Fc domain of human immunoglobulin G (IgG1). The product is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized powder cake presented in a single-use vial for intravenous (IV) administration. Each single-use vial contains one of the following; 250, 500, 750, 1000, 1500, 2000 or 3000 International Units (IU) of rFVIII Fc for reconstitution with sterile water for injection provided in a pre-filled syringe.

The Chair of the review committee requested the Division of Biological Standards and Quality Control to review the lot-release tests for the final container product (DP) as well as the potency and -b(4)----- assays for the -b(4)----- and the method validation for the same assays. This memo reports the Mid-cycle review for the lot-release assays and their validations listed above under the Summary section.

Submitted Information and Documents

This is an electronic submission. Information submitted and reviewed includes:

- 125487/0 – Cover letter, dated 07 March 2013.
- 125487/0 – 3.2.S.4 Control of Drug Substance “Specification”
- 125487/0 – 3.2.S.4.4 Batch Analyses
- 125487/0 – 3.2.P.5 Control of Drug Product “Specification”
- 125487/0 – 3.2.P.5 Batch Analyses
- 125487/0 – Application - Original BLA: Recombinant coagulation factor VIII Fc fusion protein (rFVIII Fc; Antihemophilic factor [Recombinant Fc Fusion Protein]) for the treatment of hemophilia A.
- 125487/0.7 – 1.11.1 Quality Information Amendment; Response to IR dated 31 May 2013; received 31 May 2013.

- 125487/0.7 – Gap Analysis Between –b(4)----- for recombinant Factor VIII Fc Chromogenic Potency Assay, document number B11-031-2280.
- 125487/0.7 – Addendum to Gap Analysis Between ---b(4)----- for recombinant Factor VIII Fc Chromogenic Potency Assay, document number B11-031-2280-A TR-AT-000373.
- 125487/0.7 – Development and Qualification of Factor VII Chromogenic Titer and Potency Assays for the determination of FVIII Activity in FVIII-Fc –b(4)----- document number MTR-99-08-16.
- 125487/0.7 – Linearity and Parallelism Assessment of rFVIII-Fc to the WHO 8th IS in the Chromogenic Assay, document number TR-AT-002189.
- 125487/0.7 – Transfer/Co-Validation Protocol for PRCD-25081 “rFactor VIII Fc Chromogenic Potency Assay”, document number TR-AT-002793.
- 125487/0.10 – Response to IR; Received 9 July 2013.
- 125487/0.10 – Transfer/Co-Validation Report for PRCD-25081 “rFactor VIII Fc Chromogenic Potency Assay”, document number TR-AT-003261.
- 125487/0.10 – SOP - rFactor VIII Fc Chromogenic Potency Assay, document number PRCD-25081.
- 125487/0.12 – Factor VIII-Fc aPTT and Chromogenic Variability Assessment, document number B11-031-2500.
- 125487/0.12 – Factor VIII Chromogenic AMR from August 2011 to August 2012, document number TR-QC-000738.
- 125487/0 – 3.2.S.4.2.7 Control of Drug Substance: Analytical Procedures: --b(4)-----
- 125487/0 – 3.2.S.4.3.7 Validation of Analytical Procedures – --b(4)-----
- 125487/0 – 3.2.P.5.2.13 Control of Drug Product: Analytical Procedures “Purity and Impurities”
- 125487/0 – 3.2.P.5.3.13 Control of Drug Product: Validation of Analytical Procedures – -b(4)-----
- 125487/0 – SOP PRCD 22895: Determination of Recombinant Factor VII Fc Purity by --b(4)-----
- 125487/0 – C11-031-2293-A: Validation Report for PRCD-22895: Determination of Recombinant Factor VIII Fc Purity by –b(4)-----
- 125487/0 – C11-031-2293-C: Addendum to Validation Report for PRCD-22895: Determination of Recombinant Factor VIII Fc Purity by –b(4)-----
- 125487/0.14 – 1.11.1 Quality Information Amendment
- 125487/0.18 – 1.11.1 Quality Information Amendment
- 125487/0.18 – SOP PRCD-22895 Version 7.1: Determination of Recombinant Factor VII Fc Purity by –b(4)-----
- 125487/0 – 3.2.P.5.2.9 Analytical Procedure – ---b(4)-----
- 125487/0 – 3.2.P.5.3.9 Validation of Analytical Procedures – --b(4)-----

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Method Validation

The report of a formal validation according to a protocol with pre-determined acceptance criteria was not submitted initially due to a claim by the sponsor that the method is compendial per -b(4)---. As a result, the following IR was sent to the sponsor on June 18, 2013:

You have not validated the Chromogenic Potency Assay citing that it is a compendial procedure taken from (b)(4). We do not consider those assays cited in the (b)(4) as compendial assays. Furthermore, the criticality of a potency assay precludes its consideration without appropriate method validation. Please validate this assay for the (b)(4) the drug product, and submit the validation report.

In the response to the IR received on July 09, 2013 as amendment 125487/0.10, the sponsor submitted the following method validation as reported in document # TR-AT-003261: *Transfer/Co-Validation Report for PRCD-25081 “rFactor VIII Fc Chromogenic Potency Assay”*. The method, as described in the SOP-PRCD-25081 *“rFactor VIII Fc Chromogenic Potency Assay”*, was co-validated at two sites (Biogen Iden Quality Control laboratory at Cambridge and Biogen Idec Quality Control Laboratory at –b(4)–) concurrently in compliance with ICH guideline Q2(R1) along with the method transfer. According to the product specification the DS biological activity must be –b(4)–, the DP IU/vial must be within –b(4)– of the label claim (IU/vial), and the DP biological activity must

be within --b(4)----- (proposed commercial specification) or --b(4)-----
(current specification for --b(4)-----

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Information Request

The following IR was submitted to the sponsor on 24 July 2013.

- Please provide the following two reports describing method robustness with respect to analyst, day, instrument, dilution buffer, Factor VIII deficient plasma and kit lot:
 - B11-031-2500: Factor VIII-Fc aPTT and Chromogenic Variability Assessment”.
 - TR-QC-000738: Factor VIII Chromogenic AMR from August 2011 to August 2012.

Biogen's Response: In the response to the IR received on August 07, 2013 as amendment 125487/0.12, the sponsor submitted the following two reports describing method robustness with respect to analyst, day, instrument, dilution buffer, Factor VIII deficient plasma and kit lot: "Factor VIII-Fc aPTT and Chromogenic Variability Assessment" document number B11-031-2500 and "Factor VIII Chromogenic AMR from August 2011 to August 2012" document number TR-QC-000738.

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Conclusion

Based on the evaluation of the method and the validation report, the method is suitable and validated adequately for potency and --b(4)-- testing for the 7 current DP strengths (250 IU/vial, 500 IU/vial, 750 IU/vial, 1000 IU/vial, 1500 IU/vial, 2000 IU/vial and 3000 IU/vial) as well as for both the --b(4)-----

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Based on initial review of this –b(4)----- assay, DBSQC submitted Information Requests (IR) to the sponsor on July 24, 2013. FDA received the response from the sponsor on August 7, 2013.

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4. Residual Moisture using -b(4)- -----

Residual moisture specification for the lyophilized drug product is -b(4)- for release and **-b(4)-** for stability.

Method

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Information Request

The following IR was submitted on 24 July 2013. The response by Biogen of 7 August 2013, follows each request item.

Please submit the SOP or a detailed procedural description sufficiently detailed to permit replication of the procedure. Procedural details should include the following:

- Details of sampling, --b(4)-----
- --b(4)- -----
- --b(4)- -----

Biogen Response: SOP PRCD-26652 for the Residual Moisture method and SOP PRCD-16670 for --b(4)---- use are provided. The procedures contain instructions allowing for --b(4)----
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The response has not yet been received by CBER.

Conclusion:

Review of this assay could not be completed due to an outstanding IR.

5. Polysorbate 20 --b(4)-----

Drug Product specification for the --b(4)----- Polysorbate 20 (PS-20) is --b(4)----- w/v after reconstitution of the lyophilized product with 3 mL sterile water for injection.

Method

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Information Request

The following IR was submitted on 24 July 2013. The response was received from Biogen on 7 August 2013 and has been reviewed.

Please submit the SOP or a procedural description sufficiently detailed to permit replication of the procedure.

Biogen's Response: SOP PRCD-27042 is provided

Review of Response: The SOP gives sufficient details to permit replication of the procedure. All issues have been addressed.

Conclusion:

All issues have been resolved for this assay and it is approvable for lot release of the drug product.

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1 Page determined to be not releasable: b(4)

Information Request

The following IR was submitted on 24 July 2013. The response was received on 7 August 2013 and has been reviewed.

a. Please submit SOP PRCD-32233 or let us know if the methodology utilized by --
b(4)----- SOP.

Response from Biogen: SOP PRCD-32233 was provided, which detailed the procedure for submitting samples to -b(4)----- for analysis. The actual analytical procedure, -b(4)-----, was also submitted.

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c. --b(4)-----

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The following information request was submitted on 9 October 2013: We reviewed your Quality Information Amendment submitted as Amendment 12, received on 7 August 2013, and have the following Information Request. We do not agree with your reason for not performing linearity study for Calcium Content by --b(4)----- in the product matrix. Please provide appropriate data to demonstrate linearity of the procedure in the product matrix over the proposed range of the assay.

The response has not yet been received by CBER.

Conclusion:

Review of this assay could not be completed due to outstanding an IR.

7. Reconstitution Time and Appearance of the Reconstituted Solution

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Conclusion

There is no outstanding issue for this assay and it is approvable for lot release of the drug product.

8. **-b(4)-**

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Conclusion

There is no outstanding issue for this assay and it is approvable for lot release of the drug product.