



FOOD AND DRUG ADMINISTRATION
Center For Biologics Evaluation and Research

MEMORANDUM

From: Elena Karnaukhova, Ph.D.; HFM-343; LBVB, DH, OBRR, CBER; (301) 402-4638, FAX (301) 402-2780

Subject: Review memo for analytical method validation in the Original BLA from CSL Behring (CSLB) for C1 Esterase Inhibitor (Human), C1INH, [Berinert P] for treatment of acute attacks of hereditary angioedema (HAE); 125287/0

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To the file: STN 125287/0

Action recommended:

Based on my review of analytical methods validation in the original BLA submission and taking into account the firm's responses to several CBER information requests, this part of the original BLA STN 125287 for the manufacturing of C1 Esterase Inhibitor (Human) Pasteurized [Berinert P] can be approved. However, the sponsor should provide clarification for the following:

1. Please be advised that endotoxin testing should be part of the product specifications with a justified requirement for endotoxin level. Please specify which of

EP/USP methods is utilized for endotoxin determination and what is the low detection limit of this test.

2. In order fully identify the ---b(4)----- testing by --b(4)--, please provide several actual ---b(4)---- with all ---b(4)-----.
3. Please provide typical (actual) --b(4)---- data for both release and dating period.
4. Please provide the rationale for specifically choosing aminoacetic acid (glycine) as amino acid excipient in the drug product; clarify whether determination of glycine is part of final product specifications, and how the amount added was validated.
5. We recommend that --b(4)---- testing be included in the final product specifications.
6. Please provide a copy of the final finished Product Release Specifications.
7. Validation packages for the determination of active C1INH in human serum and for anti-C1INH antibody assay (Amendment 6, Attachments 5 and 6, respectively) show that in both assays the Linearity was established over --b(4)----- . We recommend that a minimum of five concentrations should be used for the establishment of linearity (ICH Guideline Q2B (1996) for Validation of analytical procedures). If other approach is used, it must be justified.

SUMMARY

Submission date: 3-6-2008

CBER receipt date: 3-7-2008

DATS Log #: 436294

Type of submission: Original BLA, incl. 24 Amendments

Sponsor: CSLB

Product: C1 Esterase Inhibitor (Human) Pasteurized

Proprietary name: Berinert P

Indications: Treatment of acute HAE attacks

C1INH is a multi-specific serine protease inhibitor (serpin) in the circulation. It is the major inhibitor of C1s and C1r proteinases that, together with C1q protein, regulate the C1 complement complex. C1INH also inhibits the

contact system proteinases (kallikrein, XIa, and XIIa), thus regulating several pathways of inflammation, and the mannose-binding lectin-associated serpins (MASPs).

Genetic C1INH deficiencies (both functional and antigen deficiencies) may lead to life threatening HAE. The CSLB's product Berinert P is a preparation of C1INH derived from human plasma that is indicated for the treatment of acute attacks of HAE.

VALIDATION OF ANALYTICAL PROCEDURES

This memo is a review of analytical procedures validation as provided in the Modules 2 and 3 of the original BLA submission STN 125287/0 and in the Amendment 125287/0.6.

Compendial methods

Analytical procedures listed in this submission refer to the following methods as USP/CFR (or EP) compendial:

Sterility/Microbial count by -----b(4)-----

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

pH by ---b(4)-----

Ammonium sulfate determination by --b(4)-----

Pyrogens

Abnormal toxicity

Drug product quality parameters and analytical methods

Quality Attribute	Specification Requirement	Method Validation
Practibility & organoleptic properties	-----b(4)----- ----- Appearance: Colorless and clear solution	Not applicable
pH	--b(4)--	USP
Residual moisture	--b(4)--	MVR-16-345-Q617-01
Protein	--b(4)--	MVR-16-004-P617-Q617-01
--b(4)-----	--b(4)--	MVR-16-204-Q617-01

Sodium chloride	--b(4)--	MVR-16-334-Q617-Q617J-01
Sodium citrate	--b(4)--	MVR-16-048-Q617-01
----b(4)-----	--b(4)--	MVR-04-010-Q617/Q617J-01
----b(4)-----	--b(4)--	MVR-04-040-P400-01
----b(4)----- -----	-----b(4)----- ----- ----- ----- ----- ----- ----- ----- ----- -----	MVR-04-314-Q-617U-01
Purity (--b(4)--)	----b(4)----- ----- ----- ----- -----	MEV-22R
Activity	--b(4)----- ----- ----- -----	1. MVR-10-021-Q617-Q617J-01 2. MVR-10-021-Q617/Q617J/Q617U-Addendum -01
----b(4)-----	----b(4)----- -----	
Sterility	sterile	CFR/USP
Pyrogens	Pyrogen-free	CFR/USP
Abnormal toxicity	negative	CFR/USP

Testing proteins for identity and purity by ---b(4)-----
----- (MVR-04-010-Q617/Q617J-01)

Testing proteins for identity and purity by -b(4)- (by the method of ---b(4)-----) was performed using --b(4)---

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

Reviewer's comment: The data presented are acceptable,
but all copied scanned images are of low quality.

Testing for presence or absence of -----b(4)-----

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

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

---b(4)---

---b(4)---

3 Pages determined to be not releasable: b(4)

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CBER request #1: Please provide complete validation
and/or qualification packages for all central laboratory
non-routine clinical assays.

In response, the firm provided validation and qualification
packages for C1INH activity assay, C1INH antigenic
determination and C4 assay (Attachment 6).

Determination of active C1INH in human serum/plasma

Testing for active C1INH in human plasma (SOP AM-KC-124/D)
was validated for routine analysis ----b(4)-----

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Reviewer's comment: This is not a representative data set to support a validation of the parameter(s). In addition, the data were obtained using a quality control material.

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Quantitative determination of C4-complement factor in
serum/plasma

The determination of C4 is performed using --b(4)-----

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CBER request #2: Please submit the details of analytical methods (both functional and antigenic) for the determination of Cl esterase inhibitor concentrations in blood or plasma.

In addition to validation of the key parameters (above) of the functional -----b(4)-----

----- the firm provided all the package inserts and application sheets for both the commercially available equipment and the kit reagents for the CLINH activity and antigen determination (Amendment 6).

CBER request #3: Please provide a complete assay validation package for the anti-CLINH antibody assay performed by the central laboratory.

In response, the firm provided a validation package for detection of autoantibodies to CLINH by --b(4)- (Attachment 5, Amendment 125287/0.6).

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CBER request #4: **Please submit an amendment to your ongoing U.S. extension study to provide for measurement of anti-ClINH antibodies. If positive samples are obtained, it will be necessary to determine whether the antibodies are inhibitory. If positive samples are obtained, testing of baseline stored specimens may be explored to determine whether the test results were "treatment-emergent."**

In the response the sponsor clarified that there is no commercial assay available that can be used for screening serum for the presence of anti-ClINH antibodies.

The data were reviewed by the Clinical Lead. In this study the firm used an internal -b(4)- assay that was established on a request from Health Canada to test for the presence of anti-ClINH antibodies in the six Canadian subjects who were

enrolled in the pivotal clinical study no. CE1145_3001 (Attachment 4).

CMC reviewer's comment: From the CMC standpoint, currently there is no commercial assay available to determine whether the antibodies are inhibitory, and such an assay must be developed and validated. Nevertheless, it is noteworthy that all samples (from six subjects in two Canadian centers) used in this study were tested negative to C1INH antibodies.

COMMENTS

The CMC part of this BLA can be approved. However, the sponsor should provide the complete response to all CMC related questions and recommendations.