FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

FROM Omer I Butt
CBER/DH, HFM – 343

THROUGH Felice D'Agnillo, HFM – 343

TO Nannette Cagungun, HFM – 380

SPONSER LevPharma
PRODUCT C1 Esterase Inhibitor
SUBJECT Final Review Memo
STN 125267/0

Recommendation:

Based on the data provided in this submission and the updated stability data (see review of CR responses memo), a dating period of 12 months at 2-8 °C and 25-27 °C will be recommended for the final product. Sponsor has agreed to postmarketing studies to provide additional stability data on the new conformance lots of Cinryze as well as intermediates manufactured at -----(b)(4)---------- and Sanquin in Amsterdam.

Overview

The current review is for the stability testing for the product Cinryze™, a C1-esterase inhibitor. The product is being developed by the sponsor, Lev Pharmaceuticals, a New York city-based company through contract with facilities in Amsterdam and -(b)(4)--. The drug product is derived from US Source Plasma and is aimed to be used for the treatment of hereditary angioedema (HAE). HAE results due to a genetic disorder that involves endogenous C1 esterase inhibitor (C1INH), which may result in attacks of non-itching swellings of the skin or mucosa. The manufacturing overview process is described below.

The sponsor has conducted stability testing on the manufacturing intermediates and final product. In addition to the stability data provided in this submission, updated stability data was provided in response to the complete response (CR) letter which was reviewed in a separate memo.

Manufacture Overview:

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

Stability Testing Performed on:

1. ----(b)(4)---
2. ----(b)(4)---
3. ----(b)(4)----------
4. Pasteurized Planova Filtrate
5. C1-esterase-nf (Cinryze)

Proposed shelf life:

--(b)(4)--	----------
--(b)(4)--	----------
--(b)(4)----------	----------
Pasteurized Planova filtrate	----------
C1-esterase-nf	----------(b)(4)----------
	----(b)(4)----------

Stability Protocol:

Intermediates, drug substance, and drug product were tested using the following stability protocols, and the required values and limits used to pass.

[(b)(4)]

One (1) page determined to be not releasable:

(b)(4)

The addition of the 15nm Planova filters along with an additional virus removal step was added to the manufacturing process to obtain pasteurized Planova filtrates. The stability of these filtrates was tested in the same manner as earlier eluates including ----------(b)(4)----------.

No accelerated testing was performed on any of the intermediates.

C. Testing Interval

Samples were collected at the initial time point, t=0, followed by collection at 6 month intervals at 6, 12, ------(b)(4)----------.

Pasteurized Planova filtrates have been tested ------(b)(4)----------. The study will continue for --(b)(4)-----.

D. Parameters, Observations and Results

[(b)(4)]

The pasteurized Planova filtrate show passing results, with ----------(b)(4)---------- all falling within acceptable range, for the samples for which the tests were performed.

E. Comments

- No data was provided in the amendment regarding the intermediates for the conformance lots, for neither of the Amsterdam nor the -(b)(4)-- product.

- A postmarketing study will be recommended to provide additional data on the intermediates and drug substance.

Final Product
C1-inhibitor-nf

A. Lots tested

3 Lots using US source plasma [Feasibility Batches]

-------(b)(4)----------	C1-inhibitor-nf
-------(b)(4)----------	C1-inhibitor-nf
-------(b)(4)----------	C1-inhibitor-nf

3 Lots using US source plasma – Ongoing Study [Conformance lots]

-------(b)(4)----------	C1-inhibitor-nf
-------(b)(4)----------	C1-inhibitor-nf
-------(b)(4)----------	C1-inhibitor-nf

3 Lots with US source plasma – Intermediates manufactured in --(b)(4)--

-------(b)(4)----------	C1-inhibitor-nf
-------(b)(4)----------	C1-inhibitor-nf
-------(b)(4)----------	C1-inhibitor-nf

(b)(4) Lots tested for stability of reconstituted product with WFI.

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

B. Testing Conditions

- -------(b)(4)---------- will be tested for (b)(4) months at (b)(4) and also for (b)(4) months at (b)(4).

- ----(b)(4)---------- are tested according to protocol described at (b)(4)oC for (b)(4) months, and (b)(4) months at (b)(4).

- ---(b)(4)---------- will be tested for stability according to protocol for (b)(4) months at (b)(4) and (b)(4). A (b)(4) month testing would be carried out at (b)(4)°C.

- The stability of the dissolved drug with WFI was tested by dissolving the drug the drug in 5ml of water for injections and storing it at (b)(4) . The dissolved drug was tested according to protocol provided at the time intervals listed below.

C. Testing Intervals

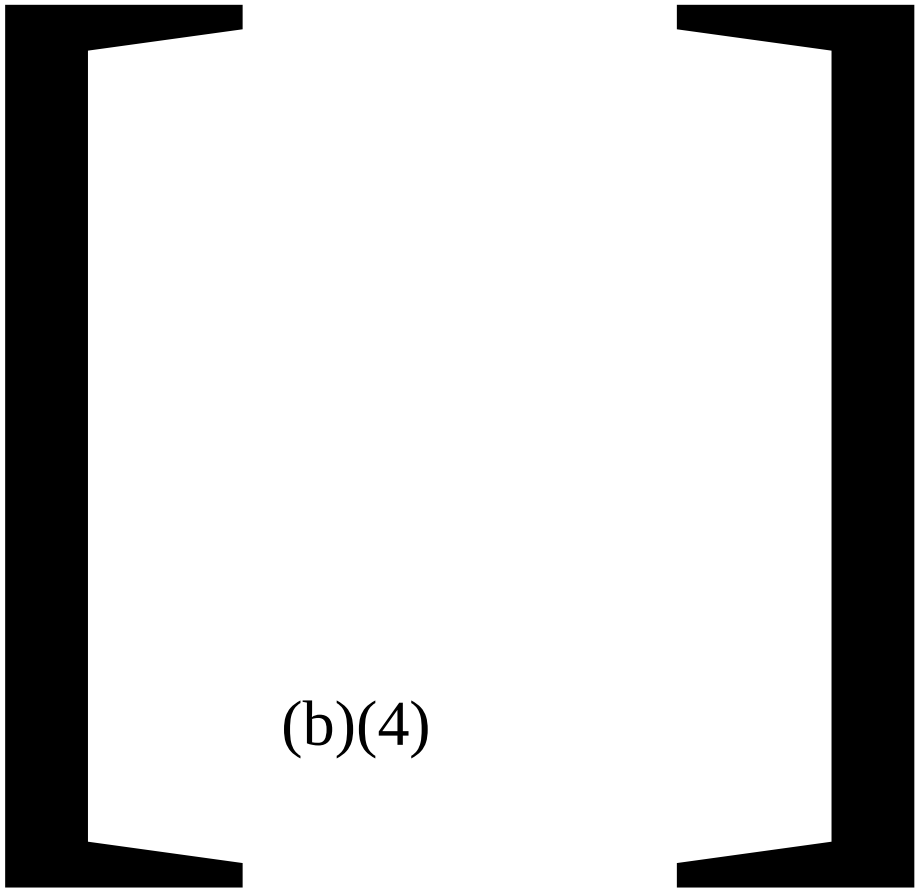
-----(b)(4) ---------- cover a stability testing period of (b)(4) months. The time points to be tested are t=----------(b)(4) ---------- Currently, (b)(4) months has been completed and submitted.

------(b)(4) ---------- are used as conformance lots, and cover a stability testing period of (b)(4) months. The time points to be tested are t=------(b)(4)----------. Currently, only (b)(4) months stability data has been completed and submitted.

----------(b)(4) ---------- were 3 batches of C1-inhibitor product, C1-esteraseremmer-N, which was equivalent to the Cetor® product with the exception of 15nm Planova filters added in series as an additional virus removal step.

The (b)(4) batches, ----------(b)(4)----------, and an additional (b)(4), ----------(b)(4)----------, were studied for the reconstitution with WFI over a (b)(4) hour time period. The time points used were t=--------(b)(4)-------.

D. Parameters, Observations and Results



The results from the WFI tests are not shown in the table, but show passing results according to the protocol and limits.

Recommended Postmarketing Studies

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

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

3. ----------(b)(4)----------.

Letter-Ready Questions

1. Regarding the (b)(4) intermediate manufacturing at the ----(b)(4)---facility, please provide updated stability data to support the proposed shelf-life for the ---(b)(4)---.

2. In your January 2, 2008 submission, you indicated that -------(b)(4) ----------(b)(4)----------. Please note that the shelf-life determination of the final product will be based on the actual real-time stability data accumulated with these lots and submitted for review prior to approval of your product.