

Reconciliation of Data on Infusions with Temporally Associated Adverse Events - Hizentra, February 26, 2010

Clinical Review Memorandum

Date: February 26, 2010

To: To File (BLA STN 125350/0)

From: Hon-Sum Ko, Medical Officer, HFM-392

Through: Nisha Jain, Acting Branch Chief, HFM-392

CC: Pratibha Rana, RPM, HFM-370

Applicant: CSL-Behring

Product: Immune Globulin Subcutaneous (Human), (IGSC, 20%; IgPro20)

Trade name: Hizentra®

Subject: Reconciliation of Data on Infusions with Temporally Associated Adverse Events

Background

CSLB's BLA on Immune Globulin Subcutaneous (Human), 20% Liquid, (IgPro20, Hizentra) was submitted on 4/30/09. At the mid-cycle review, an Information Request was conveyed to CSLB on 10/23/09, and one of the items (#8) involved infusional adverse events (AEs):

8. Please conduct an analysis of the ratio of the number of infusions with temporally associated adverse events (from start to within 72 hours of the end of infusion) to the total number of infusions, including point estimate and 95% confidence intervals.

CSLB Response on 11/12/09 (Amendment 4). *The requested confidence intervals, under inclusion / exclusion of ISRs, are provided in Table Q8.1 in Attachment 6.*

Confidence limits (CL) were calculated with the same method as described for the rate of infections in the Statistical Analysis Plan (Poisson based CL).

During the discussions on labeling for the package insert with CSLB, it became clear that the data presented in Table Q8.1 of Amendment 4 were not on the ratio of number of infusions with adverse events to all infusions, but rather the rate of infusional adverse events.

CSLB was asked to resubmit Table Q8.1 with proper information. CSLB did so with a submission on 2/22/10.

Revised Table Q8.1

In the revised Table, the number of infusions with AEs has been presented, and may be summarized as follows:

	Total no. of Infusions N=2264	
	Including local reactions	Excluding local reactions
AEs		
At least possibly related AEs		
Serious AEs		
At least possibly related serious AEs	1396 (0.617)	290 (0.128)
Temporally associated AEs (24h)	1308 (0.578)	69 (0.030)
Temporally associated AEs (48h)	9 (0.004)	9 (0.004)
Temporally associated AEs (72h)	0	0
At least possibly related, temporally associated AEs (48h)	1170 (0.517)	116 (0.051)
At least possibly related, temporally associated AEs (72h)	1328 (0.587)	140 (0.062)
At least possibly related, temporally associated AEs (72h)	1338 (0.591)	173 (0.076)
Serious at least possibly related, temporally associated AEs (72h)	1300 (0.574)	51 (0.023)
Serious at least possibly related, temporally associated AEs (72h)	1303 (0.576)	56 (0.025)
AEs, where study drug infusion had to be stopped	0	0
At least possibly related AEs, where study drug infusion has to be stopped	1 (<0.001)	0
AEs leading to withdrawal of the subject	1 (<0.001)	0
At least possibly related AEs leading to withdrawal of the subject	2 (<0.001)	1 (<0.001)
AEs leading to the death of the subject	1 (<0.001)	0
At least possibly related AEs leading to the death of the subject	0	0
At least possibly related AEs leading to the death of the subject	0	0

Thus, the ratio of infusions with temporally associated AEs (during and up to 72 hrs after the end of infusion), including local reactions, was 1338/2264 (59.1%) with 95% confidence interval of 56% and 62.4%. Excluding local reactions, the corresponding ratio was 173/2264 (7.6%) with 95% confidence interval of 6.5% and 8.9%.

The information is incorporated into labeling. The draft package insert package insert accepted by CSLB as of 2/25/10 is attached to this memo.

This memo corrects my interpretation in the Final Review Memo on BLA STN 125350/0 (dated February 16, 2010) Section 7.1, regarding infusional adverse events presented in Amendment 4.