

*Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch*

REVIEW MEMORANDUM

Date: January 15, 2010

To: Hon-Sum Ko, Medical Officer, CBER/OBRR/HFM-392
Nisha Jain, Branch Chief, CBER/OBRR/HFM-392

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Subject: **Hizentra** Immune Globulin Subcutaneous (Human)
BLA 125350
Comments on Draft Product Labeling

Background

CSL Behring (CSL) has submitted BLA 125350 for **Hizentra** Immune Globulin Subcutaneous (Human), a 20% solution of human immune globulin that will be indicated for subcutaneous use. The product is a higher concentration of CSL's marketed product, Privigen, with a new subcutaneous route of administration.

The following APLB comments address the prescribing information and patient package insert (PI and PPI) that were submitted on April 30, 2009. APLB's review also addresses the proposed carton and container labels that were submitted on November 12, 2009. Consideration is made to the medical officer's mid-cycle review dated September 28, 2009.

Comments

General

- Ensure that the proprietary name is included and is retained throughout the PI and PPI.
- Ensure that the established name, Immune Globulin Subcutaneous (Human), is the approved USAN established name. The percent solution may not be necessary in the name (see for example, Vivaglobin [Immune Globulin Subcutaneous (Human)]).
- Use command language whenever possible.
- There is excessive cross-referencing in the PI. Please revise to delete many of the unnecessary and redundant cross-references. Refrain from inordinate cross-references to the Patient Counseling Information, which is not intended to be a summarized restatement of the PI. Refrain from inordinate cross-references to Description.
- Use the term "adverse reactions" when the side effect is caused by or thought to be caused by the product. Adverse events have no known causal relationship to the product, yet are included because there is doubt. Do not include impractical adverse events that could not possibly be caused by the product.
- Refrain from using the terminology "is associated with."

Highlights Section

- The dosage form and route of administration should be on a line beneath the proprietary and proper name of the product. We have asked for an additional dosage form to be provided for infusions (SOLUTION FOR INFUSION), however this is not approved as yet. Until this occurs, the approved dosage form for immune globulin infusions would be SOLUTION FOR INJECTION.
- Because the route of administration is not typical for this dosage form, it could be confused. Thus, we recommend that “Subcutaneous Infusion Only” be added as a third line if the term “subcutaneous” is not part of the approved USAN established name.
- The boxed warning, if present, must be provided as the first subsection of the Highlights, must be in a box, and must have the bolded header

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

The verbatim statement “See full prescribing information for complete boxed warning” must be placed immediately following the header if the boxed warning presented in the Highlights is summarized (it is desirable to summarize the boxed warning in the Highlights).

- The Dosage and Administration subsection of the Highlights is too verbose and contributes to an unacceptable length of the Highlights section (half-page, not counting a 20-line boxed warning). Revise this subsection to provide only a concise summary of the dosage and administration information, including dosing regimen, starting dose, dose range, critical population differences, and monitoring recommendations. Consider using a tabular format.
- In Contraindications, the first bullet should state that proline and polysorbate 80 are among the components in Hizentra.
- The grouping of important Warnings and Precautions into the subheader “Reactions Associated with IGIV Treatment” minimizes the importance of these warnings and precautions as they relate to Hizentra itself. Similarly, discussion of any warnings, precautions, and adverse reactions as “associated with IGIV” or “as with all IGIVs” minimizes the importance of these risks to Hizentra. We recommend that the Warnings and Precautions section of the full product information (FPI) be rewritten to include each type of warning and precaution that is appropriate for Hizentra in different subsections with the correct headers. Following this revision, the Warnings and Precautions section of the Highlights should be revised to summarize the various warnings and precautions for Hizentra.
- In the Adverse Reactions subsection, please delete the statement “No serious drug-related adverse events were observed in the clinical study.” This statement implies that there was a prospectively-designed adequate and well-controlled safety study in which patients had no serious adverse reactions with Hizentra. If this is true, then there would be no warnings or precautions for Hizentra, and such is not the case.

- The list of overall common product-related adverse reactions does not appear to be consistent with the medical officer’s review of the clinical studies. Please ensure that the list is accurate.
- Add the subsection “Use in Specific Populations.” Within this subsection, a statement about use in pregnancy is required. For example

Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

Table of Contents

Revise the table of contents to be consistent with the changes to the FPI. The boxed warning must be addressed at the beginning of the table of contents

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

Full Prescribing Information

- Line 21 and Line 117: The intent of the patient counseling information section is to encourage discussion between the doctor and the patient by providing talking points. It is not a restatement of the warnings, precautions, adverse reactions, and dosage and administration. It is not an instruction manual for home use. Any patient instructions and training materials should be handled separately, and the reference to these materials should not direct the reader to the Patient Counseling Information section. In addition, the subsection “Home Treatment” should be deleted (see below).
- Revise the Dosage and Administration section to a more concise set of instructions. Use command language whenever possible and avoid detailed discussion regarding the practice of medicine. The subsection Home Treatment should not be the first subsection. If it is included at all, it should be included in Administration, following the details of administration. We suggest that the Dosage and Administration section be subdivided into 3 distinct parts:

- 2.1 Preparation and Handling
- 2.2 Dosage
- 2.2 Administration

- Revise the wording in “Preparation and Handling. The following verbatim statement should be the first bullet in this subsection:

Hizentra should be inspected visually for particulate matter or discoloration prior to administration, whenever the solution and container permit. Do not freeze. Any solution that has been frozen must not be used.

- Revise or delete the sentence “After 2 to 3 months, weekly administration of IgPro20 will lead to stable steady-state serum IgG levels with lower IgG peak levels and higher IgG trough levels compared with monthly IGIV treatment” (Lines 50-52). This statement is highly promotional and would require adequate substantiation that lower peak and higher

trough IgG levels than IGIV treatment has a beneficial outcome compared to IGIV treatments.

- In the Administration subsection of Dosage and Administration, consider adding a comment regarding the number of injection sites used in any one infusion (e.g., usual range, maximum number).
- In Contraindications, the first bullet should state that proline and polysorbate 80 are among the components in Hizentra.
- Revise the header of subsection 5.1 to “Hypersensitivity”
- A suggested order of subsections for the Warnings and Precaution section is as follows:

- 5.1 Hypersensitivity
- 5.2 Renal Dysfunction/Failure
- 5.3 Hyperproteinemia/Increased Serum Viscosity
- 5.4 Thrombotic Events
- 5.5 Aseptic Meningitis Syndrome (AMS)
- 5.6 Hemolysis
- 5.7 Transfusion-related Acute Lung Injury (TRALI)
- 5.8 Volume Overload
- 5.9 Transmissible Infectious Agents
- 5.10 Laboratory Tests

- Revise the descriptions of the reactions in each of these subsections to directly relate to Hizentra (i.e., use the name Hizentra rather than “IGSC”). For example, the descriptions should state that “[Reaction] may occur with Hizentra” or “Hizentra can contain blood group antibodies that may act as hemolysins...”
- The Laboratory Tests subsection usually is used to describe situations where there is interference with laboratory tests rather than to describe suggested monitoring. Suggestions regarding tests for monitoring may be included with the subheading for which the test is needed or may be included in Dosage and Administration.
- We suggest revising the wording for the subsection Transmissible Infectious Agents to standard language as follows

Hizentra is made from human plasma. Based on effective donor screening and manufacturing processes, it carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for Hizentra. All infections thought to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring Pharmacovigilance at 1-866-915-6958.

- List the overall common adverse reactions, with cut-off frequency at the beginning of the adverse reactions section, directly beneath the section header. Delete the sentence “No serious drug-related adverse events were observed in the clinical study.”
- Ensure that the list of most common adverse reactions is consistent with the results from the clinical studies.
- Subsection 6.1 should be entitled “Clinical Trials Experience.” Directly beneath this subsection header, place the required wording

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.

- In Line 320, please add which adverse events were judged by investigators to be “not related” to Hizentra. If it is believed that these events are not related to Hizentra, consider deleting this sentence and any unrelated events from the FPI.
- Table 4 and the associated text describe subjective reports of local injection site reaction severity. The descriptors (very slight, slight, moderate, severe) are vague and highly promotional. In the absence of quantifiable assessment or definition, such information lacks substantiation and would be highly misleading when used in promotion. We suggest that Lines 349-360 (beginning with “Table 4 summarizes the subject assessments...”) be deleted.
- The Postmarketing Experience subsection should not include events observed in the clinical trials for Hizentra.
- Revise the Patient Counseling Information section to a list of commands (bullets are suggested) that direct conversation, between the doctor or healthcare provider and the patient, that will help the patient use the product safely and effectively. This subsection is not extensive and should not have subsections. However, cross-references to certain warnings, precautions, dosage, administration, etc. may be included as needed.
- The PPI is not a subsection of the Patient Counseling Information section. It is a separate piece appended at the end of the FPI. Other patient labeling may also be appended at the end of the FPI, none should be treated as a subsection of the Patient Counseling Information section. All of the approved patient labeling must be in SPL as well.
- The manufacturer information must be included at the end of the FPI or an un-detachable PPI. If the FDA-approved patient labeling is a separate document (except in SPL), then the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling.

Patient Package Insert (PPI)

- Detailed instructions for use are usually not included in a PPI. If necessary, an *Instructions for Use* document may be approved as part of the risk management materials for home use of Hizentra.
- The target audience of the PPI is middle school level reading and math ability. If more detail is desired, the patient may be provided with the PI from the healthcare provider. Revise the wording in the PPI to be more appropriate to the target audience by making shorter sentences in command language, including easier vocabulary, refraining from mathematical terms (i.e., 20%), and bulleting long paragraphs and sections for ease of reading and comprehension.
- Since there are only two sentences in “What is the most important information I should know about IgPro20?” a bullet is not necessary.
- Consider simplifying “What is Hizentra?” For example

Hizentra (Hi – zen – tra) is a prescription medicine that is used to treat primary immune deficiency (PI). Hizentra is made from human plasma. It contains an antibody, called immunoglobulin G (IgG), that healthy people have to fight germs (bacteria and viruses).

People with PI get a lot of infections. Hizentra helps lower the number of infections that you will get.

- Consider simplifying “Who should not take Hizentra?” (This section is supposed to address the contraindications for Hizentra.) For example

Do not take Hizentra if you have too much proline in your blood (called “hyperprolinemia”).

Tell your doctor if you have had a serious reaction to other immune globulin medicines or if you have been told that you also have a deficiency of the immune globulin called IgA.

- Consider simplifying “How should I take Hizentra?” For example

You take Hizentra through an infusion under your skin. You will use up to 4 small needles that are put into different places of your body at one time. The needles are attached to a pump with infusion tubes. It usually takes about 60 minutes to do one infusion. You will need to have infusions done once a week.

There are instructions for home use of Hizentra at the end of this leaflet (see “How do I use Hizentra?”). Do not use Hizentra at home until you have been taught how to use it by your doctor or healthcare provider.

- The section “What should I avoid while taking Hizentra?” is intended to address precautions and instructions for special populations or conditions. For example

Vaccines may not work well for you while you are taking Hizentra. Tell your doctor or healthcare provider that you are taking Hizentra before you get a vaccine.

Tell your doctor or healthcare provider if you are pregnant, plan to become pregnant, or if you are nursing.

- The section following “What should I avoid while taking Hizentra?” is the section entitled “What are the possible of reasonably likely side effects for Hizentra?” This section should be a simple bulleted list of the common side effects followed by statements regarding potentially serious side effects for which the patient should call the doctor or healthcare provider. For example

The most common side effects with Hizentra are

- Redness, swelling, and itching at the injection site
- Headache/migraine
- Cough
- Stomach ache
- Diarrhea
- Nausea
- Rash
- Joint pain
- Fatigue
- Nose Bleed

Tell your doctor right away or go to the emergency department if you have hives, trouble breathing, wheezing, dizziness, or fainting, because these could be a signs of a bad allergic reaction.

Tell your doctor right away if you have any of the following symptoms because they could be signs of a serious problem

- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. (Because these could be signs of a brain swelling called meningitis.)
- Reduced urination, sudden weight gain, or swelling in your legs. (Because these could be signs of a kidney problem.)
- Brown or red urine, fast hard rate, yellow skin or eyes (Because these could be signs of a blood problem.)
- Pain, swelling, warmth, redness or a lump in your legs or arms. (Because these could be signs of a blood clot.)
- Chest pains or trouble breathing.
- Fever over 100°F (Because this could be a sign of an infection.)

Talk to your doctor about any side effects that concern you. You can ask your doctor for more information that is available to healthcare providers.

- Using the examples above, simplify the section “How do I use Hizentra?” This section **MUST** be made more patient-friendly to avoid misuse. It must have simple, easy-to-follow steps with figures (the figures have not been provided for comment) and must avoid long explanations with too much information. The vocabulary must be simplified as well.

Delete Lines 808-817 and replace with

Infuse Hizentra at home only after you have been trained by your doctor or healthcare provider. Below are step-by-step instructions to help you remember how to use Hizentra. Ask your doctor or healthcare provider about any instructions that you do not understand.

Follow this introduction with steps defined as “Step 1, Step 2, Step 3, etc.” (use the steps instead of additional headers in this section).

Delete Lines 818-831

Revise Lines 832-838 to

Hizentra comes in single-use vials.
Store Hizentra in the storage box at room temperature.

Step 1. Gather supplies needed

Following the list of supplies, describe hand washing (Lines 855-856) as

Step 2. Wash hands.

Follow this with a description of how to clean the table (with the alcohol wipe) under

Step 3. Clean table or non-porous flat surface

Follow this with the process of checking for particulate matter and preparation of vials

Step 4. Check vials

Follow this with the directions for transferring Hizentra from vial to syringe

Step 5. Transfer Hizentra to syringe for infusion

Delete the phrase on Line 873 “Using aseptic technique as instructed by your healthcare professional”

Delete Lines 890-891. The healthcare professional should have already said everything that needs to be said and the patient is trained. If this is inadequate, then include instructions for a second vial.

Follow this with the directions of pump preparation and priming of the infusion tubing (Replace the term “administration tubing” with “infusion tube”)

Step 6. Prepare pump and infusion tubing

The next step should include all information about injection site selection and preparation

Step 7. Prepare injection site(s)

The sentences from Lines 900-901 should be the first bullet for Step 7.
Delete Lines 903-904

Follow this step with **Step 8. Insert needle(s)**

In Step 8, include sticking the needles in, checking for blood, and securing the needles as bullets.

The final 4 steps are

Step 9. Start infusion

Step 10. Record treatment in diary or logbook

Step 11. Clean up

Include the following information in Step 11: “Throw away any Hizentra that is leftover in the single-use vial.”

- For Lines 949-950, side effect reporting from the patient should be either through the physician or directly to MedWatch. Do not include CSL’s phone number. Revise these lines to read

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

- Delete Lines 952-953. CSL Behring may not promote discussion of product information between the patient and their medical affairs department.
- Delete Line 955: We do not include product websites in FDA approved labeling. Information in a product website is promotion and is not pre-approved by FDA. However, the sponsor is required to provide the website and any website modifications upon first use on FDA Form 2253.

Carton and Container Labels

- Delete enrollment information for “1-888-Update-U” from the outer carton labels.
- Abbreviations, such as “SC,” have been the source of medication errors (see IMSP guidelines). Please use the entire word, “subcutaneous,” rather than the abbreviation.

The above comments are provided from a comprehension and an advertising and promotional labeling perspective to assist you in revising the proposed labeling materials. If you have any questions, please contact Lisa Stockbridge at 301-827-6226.

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