



U.S. FOOD & DRUG
ADMINISTRATION

Memorandum

DATE: November 5, 2018

TO: Michael Kennedy, Chair, CBER OTAT/DPPT/PDB
Edward Thompson, RPM, CBER/OTAT/DRPM/RPMBII

FROM: Stephanie Donahoe, R.Ph., MPH
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THROUGH: Lisa L. Stockbridge, Ph.D.
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SUBJECT: **CUTAQUIG (immune globulin subcutaneous, human- hipp)**
BLA: 125668/0
Sponsor: Octapharma

Background

The sponsor submitted:

- ☒ New Approval
- ☐ Changes Being Effected (CBE) supplement
- ☐ Prior Approval Supplement (PAS)
- ☐ Major Amendment

Submission contains:

- ☒ Prescribing Information (PI)
- ☒ Patient Package Insert (PPI)
- ☒ Package and/or container labels
- ☒ Other (Instructions for Use, etc.)

Submission Date: December 29, 2017

PDUFA Action Date: December 29, 2018

APLB Comments/Recommendations

On December 29, 2017, FDA received Octapharma's Biologics License Application for **CUTAQUIG (immune globulin subcutaneous, human – hipp)**, a 16.5% solution for subcutaneous use, indicated for treatment of primary immunodeficiency (PI) in adults.

APLB received SharePoint access to the initial edits to the prescribing information on October 17, 2018, and the medical officer's draft review on October 31, 2018.

APLB reviewed the proposed labeling edits dated November 1, 2018, as well as package and container labels submitted on December 29, 2017, and concurs with the edits except for the following comments and observations, provided from a promotional and comprehension perspective:

GENERAL

- In all labeling, update the proper name to include the suffix:

CUTAQUIG (immune globulin subcutaneous, human - hipp)

- The lowercase, stylized registered trademark of this product is not its proprietary name. The proprietary name, **CUTAQUIG**, should appear in upper case letters, as it does in most SPL stylesheets. For consistency, please capitalize the proprietary name throughout the **FULL PRESCRIBING INFORMATION (FPI)**.
- The product proprietary and proper names, dosage form, and route of administration constitute the "product title" (see *Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format*), which appears on the same line and can continue to another line in the **HIGHLIGHTS**. The standard for the dosage form of this product is: injection, for subcutaneous use. However, *subcutaneous* is in the proper name. Delete the word "liquid," as it is not any standard and it is redundant to "solution." The solution strength is not part of the proper name or the product title, but there is precedent to use it for immune globulin solutions.

There is no precedent for using "solution for subcutaneous use" with immune globulins; but, there is precedent for including the concentration (e.g., HIZENTRA, immune globulin subcutaneous (human) 20% liquid; HYQVIA [immune globulin infusion 10% (human) with recombinant human hyaluronidase] Solution for subcutaneous administration; CUVITRU, immune globulin subcutaneous (Human), 20% Solution). In an effort to try to move toward the regulations and guidance, while maintaining product title precedence for immune globulins, we suggest that the product title appear as follows:

CUTAQUIG (immune globulin subcutaneous, human - hipp), 16.5% solution

- Use bold headings only when required by the regulations. Underlining or italics can be used alternatively.
- Consistently use *one* term when describing the following: health care professional, doctor, physician, or health care provider.
- When using an acronym, spell it out at the start of each labeling section. Each section must be able to stand on its own because sections can be commuted in different SPL stylesheets.
- To improve comprehension and readability, use active voice wherever possible.
- The FPI and PPI have many minor typographical errors, particularly omission of punctuation.

BOXED WARNING

The **BOXED WARNING** for this class of products includes thrombosis, renal dysfunction and acute renal failure. Revise to be consistent with the class.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Revise the indications statement to the regulatory language, including the product class, as follows:

CUTAQUIG (immune globulin subcutaneous, human – hipp) is a 16.5% immune globulin solution for subcutaneous injection indicated for the treatment of primary immunodeficiency in adults.

DOSAGE AND ADMINISTRATION

- Revise the route of administration statement to sentence case: **For subcutaneous use only.**
- This section should emphasize that patients must be stabilized on intravenous immune globulin (IGIV) before initiating CUTAQUIG. Consider placing this information, along with the statement, “Before switching to CUTAQUIG, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments,” prior to the subsections **Dose** or **Administration**.
- Remove the sentence regarding administration interval that is directly beneath the bolded route of administration sentence. This is inhibiting readability for the Dose information (which should be entitled “Dose,” not “Dosage”). Administration interval belongs under administration.

WARNINGS AND PRECAUTIONS

- **WARNINGS AND PRECAUTIONS** in the **HIGHLIGHTS** should summarize information in the FPI. These summaries may be shorter if it is necessary to keep the HIGHLIGHTS to its half page limit (BOXED WARNING not counted for this limitation).
- Verify that the **WARNINGS AND PRECAUTIONS** are listed in a manner consistent with the product class, in order of severity and public health significance. For example
 - Hypersensitivity and anaphylactic reactions can occur with CUTAQUIG. IgA deficient patients with antibodies against IgA are at greater risk of developing severe reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions. (5.1)
 - Thrombosis may occur with CUTAQUIG (5.2)
 - Aseptic Meningitis Syndrome (AMS) may occur within two days of treatment. (5.3)
 - Monitor patients for signs and symptoms of renal dysfunction. (5.4)
 - Hemolysis, either intravascular or due to enhanced RBC sequestration, can develop. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia, especially in patients with pre-existing anemia and/or cardiovascular or pulmonary compromise. (5.5)
 - Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.6)
 - CUTAQUIG is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.7)
 - Passive transfer of antibodies may confound serologic testing. (5.8)*

*We note that passive transfer of antibodies (a class precaution) is missing from the current WARNINGS AND PRECAUTIONS section of CUTAQUIG. This is in DRUG INTERACTIONS but appears in this section in other class labels. Consider adding it to this label.

DRUG INTERACTIONS

Delete the bullet notation as there is only one item. Use bullets when there are at least two items in a list.

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure that the **FULL PRESCRIBING INFORMATION: CONTENTS** aligns with the sections and subsections of the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION (FPI)

BOXED WARNING

The **BOXED WARNING** should be consistent with the class (see comment above regarding contents).

2 DOSAGE AND ADMINISTRATION

- Replace, “**For subcutaneous administration only**” with “**For subcutaneous use only.**” Do not include statements about routes of administration that are not used for the product, as these can be read quickly as an alternative route.
- Emphasize that patients must be stabilized on IGIV before switching to CUTAQUIG. Consider this information as a statement under the section heading in addition to its placement under the subsection **Administration**. This does not belong under “2.2 Dosage.”
- For consistency with most products in this class and similar, as well as ease in SPL style sheet interoperability, consider using the following subsections and subsection headings for this section:

2.1 Dose

2.2 Preparation

2.3 Administration

- This section has reduced readability because of overuse of passive voice, particularly in the sub-subsections entitled “Dosage for patients switching to CUTAQUIG from another immune globulin subcutaneous (Human) Treatment (IGSC)” of the subsection currently entitled “Dosage.” The subsection also has information that belongs in other subsections.
- Consider “Dose Adjustment” to be a main sub-subsection heading under **2.1 Dose**. Its current position, near the end of this subsection, creates a disorganization. For example, the last paragraph, regarding switching from another IGSC product is now not beneath a current sub-subsection that is named, “Dosage for patients switching to CUTAQUIG from another Immune Globulin Subcutaneous (Human) Treatment (IGSC)”
- Sub-subsections cannot be in bolded type font. Choose italics or underlining.
- Make sub-subsection headings more succinct. The wordiness is reducing readability.
- The sub-subsection on dosing following measles exposure constitutes a new indication of this product and can be promoted as such. If this product is indicated for measles prophylaxis, then it must also be in **INDICATIONS AND USAGE**.

5 WARNINGS AND PRECAUTIONS

- Ensure that the product name, CUTAQUIG, is associated with risk phrases that involve class warnings and precautions. By not including the product name, the risk association with the product is minimized. Consider the following

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur **with CUTAQUIG**, ...

5.3 Aseptic Meningitis Syndrome (AMS)

Aseptic Meningitis Syndrome (AMS) can occur with CUTAQUIG. AMS has been reported after the use of human immune globulin administered either intravenously or subcutaneously. It usually begins a few hours to two days following treatment, and occurs more frequently in females than males. ...

6 ADVERSE REACTIONS

- Delete references to “adverse events.” Only adverse reactions belong in **6 ADVERSE REACTIONS**. Events known or suspected to be related with CUTAQUIG are its “adverse reactions,” a term defined in the regulations, as defined in 21 CFR 201.5(c)(7).
- Avoid the terms such as “Phase 3” and “pivotal” because they are not easily defined, vague or promotional in tone. Instead, describe as a major effectiveness study.
- Avoid vague terms such as “mild” or “moderate” that do not have established definitions.
- The statement “No AE led to withdrawal of subject from the study and none led to discontinuation of the study medication,” is promotional and should be deleted.
- Include the following required language under **6.2 Postmarketing Experience**:

There is no postmarketing experience with CUTAQUIG. The following adverse reactions have been identified during post approval use of immune globulins. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **6.2 Postmarketing Experience** focuses on domestic and foreign spontaneous reports that are not addressed anywhere else in the risk information of the FPI. Do not include adverse reactions reported under the 6.1 Clinical Trials Experience subsection.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Use international English spellings, for example, replace “foetal” with “fetal.”
- Delete this sentence as it is not informative: *CUTAQUIG should be given to a pregnant woman only if clinically indicated.*

8.4 Pediatric Use

Delete the sub-subheading “Clinical studies,” as there is not enough information for the extra heading, and it reduces readability.

8.5 Geriatric Use

This subsection has regulatory language for instances where there are little or no data on geriatric patients. The situation for CUTAQUIG would have the following language:

Clinical studies of CUTAQUIG did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

12 CLINICAL PHARMACOLOGY

Subsection **12.2 Pharmacodynamics** is required. This subsection describes biochemical or physiological pharmacologic effects of the product or active metabolites, with respect to clinical effect, adverse reactions, or toxicity.

13 NONCLINICAL TOXICOLOGY

- This section heading is not hyphenated.
- Increase readability for subsection 13.2 by instituting a parallel list. It is unnecessary to keep repeating the proprietary name of the product.

14 CLINICAL STUDIES

- Avoid the terms such as “Phase 3,” “primary endpoint,” and “secondary endpoint.” Instead, describe only those endpoints that were found to be both statistically and clinically significant or demonstrated a meaningful lack of effect.
- Further describe the study population in terms of ethnicity as outlined under 21 CFR 201.57 (c)(15), if the information is available.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Overuse of the proprietary name reduces readability in this section. Delete the proprietary names in the bullets.
- Use active voice.
- Given the weight of each single use vial, is there concern that the various products provide different concentrations when the math is computed as follows?:

1gm/6ml =	0.167gm/ml =	16.7mg/ml*
1.65gm/10ml =	0.165gm/ml =	16.5 mg/ml
2gm/12ml =	0.167gm/ml =	16.7mg/ml*
3.3gm/20ml =	0.165gm/ml =	16.5 mg/ml
4gm/24ml =	0.167gm/ml =	16.7mg/ml*
8gm/48ml =	0.167gm/ml =	16.7mg/ml*

17 PATIENT COUNSELING INFORMATION

Consider adding the following to the Home treatment/Self administration subsection:

- Inform patients to be tested regularly to make sure they have the correct levels of CUTAQUIG (IgG) in their blood. These tests may result in adjustments to the CUTAQUIG dose.

PATIENT PACKAGE INSERT (PPI)

- The dense paragraph form, high level vocabulary, and indirect sentence structures of this PPI will reduce readability. Revise this PPI to “patient-friendly” language.
- Pick a term for healthcare provider and stay consistent with the term throughout the PPI.
- Revise “Who should NOT use CUTAQUIG?” as follows (the “tell your doctor what drugs...” statement belongs in “What should I tell my healthcare provider before using CUTAQUIG”:

Do not use CUTAQUIG if you have ever had a severe allergic reaction to immune globulin or other blood products.

Tell your doctor if you:

- ever had any severe reaction to other immune globulin medicines.
- were told that you have a condition called “IgA deficiency.”
- have a history of heart or blood vessel disease.
- get blood clots or have “thick blood.”
- have had restricted movement for some time.

INSTRUCTIONS FOR USE (IFU)

APLB has no additional comments on the IFU.

CONTAINER AND PACKAGE LABEL

- Ensure that the colors on the container and package labels are sufficiently different. For example, the 1.65 and 8 gram strengths appear indistinguishable on the computer screen and on printed hard copy (designated as Panton Reflexblue; and Pantone Cool Gray 11, respectively).
- Update the proper name on the labels to include the suffix.

If you have any questions regarding this review, please contact Stephanie Donahoe, Consumer Safety Officer at 240-402-9557.

Firm name: Octapharma

Product: CUTAQUIG

File name: CUTAQUIG_LR_125668 0.doc

History

Prepared:	Stephanie Donahoe	9/28/18
Comments:	Alpita Popat	10/22/18
Revised:	Stephani Donahoe	10/23/18
Comment:	Lisa Stockbridge	10/30/18
Final:	Lisa Stockbridge	11/05/18

Concurrence box:

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