Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Shaokui Wei, MD, MPH Epidemiologist, Pharmacovigilance Branch 3 (PB3) Division of Pharmacovigilance (DPV), OBPV, CBER
Through:	Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Octapharma Pharmazeutika Produktionsges.m.b.H.
Product:	Cutaquig (Immune Globulin Subcutaneous (Human) - hipp)
STN:	BLA 125668/371
Indication:	Cutaquig is a 16.5% immune globulin solution for subcutaneous infusion (IGSC), indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
Meeting Date:	Pediatric Advisory Committee Meeting, 2024

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of the supplemental Biologics License Application (sBLA 125668/158), on October 22, 2021, to extend use in children 2 to <17 years of age for treatment of primary humoral immunodeficiency.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

Cutaquig is a 16.5% immune globulin solution for subcutaneous infusion (IGSC), indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Cutaquig is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. Cutaquig is a solution for injection to be administered subcutaneously and is supplied in 6, 10, 12, 20, 24, and 48 mL vials.

1.3 Regulatory History

- December 12, 2018: Initial FDA approval of BLA 125668/0 for treatment of PI in adults.
- October 22, 2021: FDA approval of sBLA125668/158 to extend the indication for use in children 2 to <17 years of age for treatment of PI
    - Trigger for current PAC review, subject of this memorandum

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS) reports for Cutaquig during October 22, 2021 to October 31, 2023 (safety review period)
- Manufacturer's submissions
    - Cutaquig U.S. package insert; Revised: 11/2021
    - Applicant response to information request regarding dose distribution data, received December 4, 2023

    - U.S. Pharmacovigilance Plan (Risk Management Plan (RMP), version 01.2a and U.S. Addendum version 03 (data lock point November 30, 2020)
    - Periodic safety reports
- FDA Documents
    - Cutaquig BL 125668/158 approval letter
    - Cutaquig BL 125668/158 Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety related labeling changes during October 22, 2021 to October 31, 2023.

4 PRODUCT UTILIZATION DATA

Octapharma provided the following estimates of Cutaquig distribution data for the U.S. and worldwide for the safety review period.

- U.S. distribution data for Cutaquig during November 1, 2021, to October 31[1], 2023:
- U.S. distribution date for Cutaquig since initial U.S. licensure (December 12, 2018) to October 31, 2021:
- Worldwide distribution data for Cutaquig during November 1, 2021, to October 31, 2023[1]:
- Worldwide distribution data for Cutaquig since December 1, 2018, to October 31, 2021:

As per the package insert, the recommended dose of Cutaquig is calculated based on patient's serum Immunoglobulin G (IgG) trough level, and the dose is individualized based on the patient's pharmacokinetic and clinical response.

The sponsor, Octapharma, reported that they have no access to information about the breakdown of patient exposure in the pediatric age group (< 18 years) versus adults (> 18 years and older).

These data were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

[1]As per sponsor, due to administrative reasons reporting time period for the distribution data had to be set to "November 01, 2021, to October 31, 2023" instead of October 22, 2021 to October 31, 2023.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The current Pharmacovigilance Plan (PVP) for Cutaquig, RMP, version 1.2a and U.S. Addendum version 03, 09-Jun-2021, lists the following important identified and potential risks, and missing information (see Table 1).

Table 1: Cutaquig Safety Concerns

Important Identified Risks
Hypersensitivity reactions, including anaphylactic reactions
Thromboembolic events
Aseptic meningitis
Renal dysfunction/failure
Hemolysis
Important Potential Risks
Transfusion-related acute lung injury (TRALI)
Suspected transmission of pathogen infection
Missing Information
Safety in pregnant or breastfeeding women

The important identified and potential risks for Cutaquig are labeled events and consistent with the safety profile of other immune globulin products. The USPI describes Hypersensitivity, Thrombosis, Aseptic Meningitis Syndrome, Renal Dysfunction/Failure, Hemolysis, Transfusion-related Acute Lung Injury (TRALI), and the risk for Transmittable Infectious Agents under Warnings and Precautions section. Thrombosis is also included as a boxed warning in the USPI.

The important identified and potential risks listed in Table 1 are monitored with routine pharmacovigilance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement or commitment (PMR/PMC) safety studies or Risk Evaluation and Mitigation Strategy (REMS) for Cutaquig.

5.2 Postmarketing Studies

The following postmarketing studies were described in BL 125668/0 approval letter dated December 12, 2018.

<u>Postmarketing requirement under Pediatric Research Equity Act (PREA)</u>

“This is a deferred pediatric study (protocol SCGAM-01) under PREA for the treatment of primary humoral immunodeficiency in pediatric patients ages two to < 17 years of age. The study provides pharmacokinetic data for at least two subjects ages two to < 6 years, at least six subjects ages six to < 12 years, and at least four subjects ages 12 to

< 17 years of age, as well as safety and efficacy data for at least four subjects ages two to < 6 years, at least 10 subjects ages six to < 12 years, and at least six subjects ages 12 to < 17 years of age. The final report compares efficacy and safety between pediatric age cohorts and between pediatric and adult subjects included in the study.

Final Protocol Submission: January 31, 2019
Study Completion Date: August 31, 2020
Final Report Submission: December 31, 2020”

Reviewer comments: The above pediatric study was completed and the data from this study supported the approval of sBLA125668/158 to extend the indication for use in children 2 to <17 years of age for treatment of PI (trigger for this PAC review).
The applicant has fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Cutaquig between October 22, 2021 (approval of sBLA 125668/158 and trigger for this PAC review) to October 31, 2023 (data lock point). FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of AE reports for Cutaquig during the safety review period are listed in Table 2 below. There were 43 reports, including 24 U.S. and 19 foreign reports for the safety review period October 22, 2021 to October 31, 2023.

Table 2: Cutaquig FAERS reports during safety review period (October 22, 2021 to October 31, 2023)

Age	Serious Non-Fatal	Deaths	Non-Serious	Total Reported

	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<17 years	0	0	0	0	0	0	0	0
≥ 17 years	3	15	0	1	4	0	7	16
Unknown	7*	3*	0	0	10	0	17	3
All Ages	10	18	0	1	14	0	24	19

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).
*Note that upon manual review of narratives for individual reports, additional information was obtained on age (please see section 6.2.2).

6.2.1 Deaths

There was one (1) death reported during the safety review period October 22, 2021, to October 31, 2023. A 72-year-old male patient received Cutaquig for secondary immunodeficiency on May 20, 2021. The patient died on January 2, 2022; cause of death was reported as “unknown cause”.

6.2.2 Serious Non-fatal Reports

There were 28 serious non-fatal reports. During manual review of narratives for individual reports, additional information was obtained on age and it was ascertained that there were 23 adult reports and age was unknown for the remaining 5 reports. No reports specifically involved pediatric patients.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for adult reports and reports in patient of unknown age are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for serious non-fatal reports

Preferred Tern (PT)	**# Serious Reports**	**Label Status** *USPI updated:11/2021 (Label Section)*
Headache	5	Labeled (5.4), (6.1)
Nausea	3	Labeled (6.2)
Pyrexia	3	Unlabeled*
Abdominal distension	2	Labeled (6.2)
Burning sensation	2	Unlabeled*
COVID-19	2	Unlabeled**
Dyspnoea	2	Labeled (6.2)
Injection site necrosis	2	Labeled (6.2)
Injection site pain	2	Labeled (6.2)
Pain	2	Labeled (6.2)
Pain in extremity	2	Unlabeled, but related to labeled event “pain” (6.2)
Peripheral swelling	2	Unlabeled, but related to labeled event “swelling” (6.1)

Preferred Tern (PT)	# Serious Reports	Label Status *USPI updated:11/2021 (Label Section)*
Pruritus	2	Unlabeled*

* Unlabeled PT is a non-specific event

** Unlabeled, but related to infection and therefore confounded by indication

Label section: 5 Warnings and Precautions, 5.4 Aseptic Meningitis Syndrome (AMS); 6 Adverse Reactions, 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience

Reviewer comments: Most PTs are labeled events or consistent with a labeled event.

6.2.3 Non-serious Reports

During the reporting period, there were 14 non-serious reports; no reports involved pediatric individuals. Table 4 below lists the most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Ten most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status *USPI updated:11/2021 (Label Section)*
Headache	3	Labeled (5.4), (6.1)
Nausea	3	Labeled (6.2)
Abdominal pain	2	Labeled (6.2)
Aphasia	2	Unlabeled
Dizziness	2	Labeled (6.2)
Pruritus	2	Labeled (6.2)
Rash	2	Labeled (6.1)

Label section: 5 Warnings and Precautions, 5.4 Aseptic Meningitis Syndrome (AMS); 6 Adverse Reactions, 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience

Reviewer comments: Most PTs are labeled events. The unlabeled PT for *Aphasia* was reviewed and based on a duplicated report for one unique patient, a 55-year-old female who presented with hypertension, cryptogenic stroke, and hyponatremia. She received her first treatment with Cutaquig on 05-Nov-2022 and experienced nausea and dizziness. It was reported that she felt her thoughts were not clear and that she had difficulty finding words which later resolved after eating. Her unclear thoughts and aphasia might be due to hyponatremia which was likely caused by overhydration before/during her infusion. The symptoms of aphasia were not noted on her second and third infusion after restricting fluids.

There are no new safety concerns from review of most frequently reported PTs in non-serious reports.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Cutaquig were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point as of December 3, 2023. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified the PTs summarized in Table 5, with a disproportional reporting alert. Note that a report may have one or more PTs. (Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 5: Data mining findings

Preferred Term (PT)	**# Reports**	**Label Status** *USPI updated:11/2021 (Label Section)*
Headache	12	Labeled (5.4), (6.1)
Nausea	13	Labeled (6.2)
Sinusitis	5	Unlabeled**

** Unlabeled, but related to infection and therefore confounded by indication

Label section: 5 Warnings and Precautions, 5.4 Aseptic Meningitis Syndrome (AMS); 6 Adverse Reactions, 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience

Reviewer comments: Most PTs are labeled events or consistent with a labeled event and are also represented among the most common PTs for serious and non-serious reports (please see discussion in sections 6.2.2 and 6.2.3).

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Cutaquig were reviewed. The AEs reported were consistent with those seen in FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on December 3, 2023, for peer-reviewed literature, with the search term "Cutaquig" and "safety" limited by human species, and dates from PAC trigger (October 22, 2021) to date of search (December 3, 2023), retrieved 3 publications pertaining to safety. No new safety concerns for Cutaquig were identified in the review of these publications, summarized in the table below:

Publication	**Authors' Safety Conclusion**
Kobayashi RH, Litzman J, Melamed I, Mandujano JF, et al. Long-term efficacy, safety, and tolerability of a subcutaneous	This prospective, long-term study showed that Cutaquig maintained efficacy and low rates of local and

immunoglobulin 16.5% (Cutaquig®) in the treatment of patients with primary immunodeficiencies. Clin Exp Immunol. 2022 Dec 15;210(2):91-103.	systemic adverse reactions in PID patients over up to 238 weeks of follow-up.
Gupta S, DeAngelo J, Melamed I, Walter JE, et al. Subcutaneous Immunoglobulin 16.5% (Cutaquig®) in Primary Immunodeficiency Disease: Safety, Tolerability, Efficacy, and Patient Experience with Enhanced Infusion Regimens. J Clin Immunol. 2023 Aug;43(6):1414-1425.	SCIG 16.5% (Cutaquig®), infusions are efficacious, safe, and well tolerated with reduced infusion time, fewer infusion sites, and reduced frequency.
Gupta S, Kobayashi RH, Litzman J, Cherwin L, et al. Subcutaneous immunoglobulin 16.5% for the treatment of pediatric patients with primary antibody immunodeficiency. Expert Rev Clin Immunol. 2023 Jan;19(1):7-17.	The safety, efficacy, and tolerability of SCIG 16.5% have been demonstrated in pediatric patients with PIDs providing an additional therapeutic option in this vulnerable population.

8 CONCLUSION

This postmarketing pediatric safety review for Cutaquig was triggered by the approval of sBLA 125668/158, on October 22, 2021, to extend use in children 2 to <17 years of age for treatment of primary humoral immunodeficiency.

Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and published literature does not indicate any new safety concerns. There were no pediatric AE reports. Adverse events were generally consistent with the safety data in pre-licensure studies listed in the label. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Cutaquig.