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 Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
From:	Shaokui Wei, MD, MPH Epidemiologist, Analytic Epidemiology Branch (AEB), DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Baxalta US, Inc.
Product:	Cuvitru, Immune Globulin Subcutaneous (Human) (IGSC), 20% Solution
STN:	125596/492
Indication:	Indicated for use in replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older.
Meeting Date:	Pediatric Advisory Committee Meeting, April 2021

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 is the initial approval of Cuvitru indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients two years of age and older on September 13, 2016.

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

1.2 Product Description

Cuvitru is an immune globulin subcutaneous (human) (IGSC), 20% solution indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients two 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. Cuvitru is manufactured from large pools of human plasma. It is supplied in single use vials containing the labeled amount of functionally active IgG.

1.3 Regulatory History

September 13, 2016: Initial approval of Cuvitru BLA 125596/0 indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older **(**trigger for PAC**)**

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Cuvitru during September 13, 2016 to September 30, 2020
- Manufacturer's Submissions
    - Cuvitru, U.S. package insert, updated July 22, 2019
    - Applicant response to information request regarding dose distribution data
    - Applicant response to information request dated November 27, 2020 regarding increased number of FAERS reports for Cuvitru since October 2019
    - Pharmacovigilance Plan, version 1.0, dated September 1, 2015
    - Periodic safety reports
- FDA Documents
    - BLA 125596/0 Cuvitru Approval Letter, dated September 13, 2016

    - o BLA 125596/0 OBE/DE Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA[1]

Takeda provided distribution data for the U.S. and outside of the U.S. for the period of January 1, 2017 to September 30, 2020.

US distribution of Cuvitru from January 1, 2017 to September 30, 2020 was (b) (4) grams. Takeda stated that due to the limitation in collecting sales data, it is not possible to estimate patient exposure in the pediatric age group (<18 years) versus adults (18 years and older).

Using the distribution data above, a rough estimate of doses would be (b) (4) doses. (As per the package insert, the weekly dose of Cuvitru is recommended to be the same as the weekly dose of prior immune globulin subcutaneous (IGSC) treatment. Since dose is based upon weight, indication, and clinical response, these figures are only general estimates. The figure is based on the typical dose of 0.3g/kg for a 70kg adult for treatment of primary humoral immunodeficiency. The actual number of doses administered could be substantially lower or higher depending on the amount of product that was distributed but not yet administered, the amount of use in pediatric patients, the route used, and the dosage administered.)

Worldwide distribution of Cuvitru from January 1, 2017 to September 30, 2020 was (b) (4) grams. Takeda did not have any reliable information to project/estimate product distribution by age outside of the US.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP), Version 1, dated September 1, 2015, lists the following important identified risks, important potential risks, and missing information (see Table 1);

Table 1: Cuvitru safety concerns

Important Identified Risks
Interference with serological tests after infusion of immunoglobulins
Altered immune response and implication for laboratory testing

[1] Distribution data is protected as confidential commercial information and may require redaction from this review.

Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella
Important Potential Risks
Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies
Hemolysis/Hemolytic anemia
Thromboembolic events
Transmission of infectious agents
Severe renal adverse reactions including renal failure
Aseptic meningitis syndrome
Missing Information
Lack of information on safety in pregnant and lactating women
Limited information on the safety in neonates or infants <2 years old
Limited information in patients with organ impairment (e.g., kidney, liver, or cardiac)
Limited information on safety in elderly patients 65 years and older

The identified and potential risks for Cuvitru listed in the above table are common to the immune globulin product class and are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no ongoing or planned additional pharmacovigilance activities, postmarketing safety study, or Risk Evaluation and Mitigation Strategy(REMS) proposed..

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Cuvitru received between September 13, 2016 (PAC trigger) and September 30, 2020 (data lock point for this review). 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 adverse event reports for Cuvitru during the review period are listed in Table 2. There were 2,763 U.S. and 101 foreign reports.

Table 2: FAERS reports for Cuvitru (September 13, 2016 – September 30, 2020)

Age (years)	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18	27	1	0	0	37	0	64	1
≥18	274	6	20	0	267	0	561	6
Unknown	600	78	16*	12*	1522	4	2138	94
All ages	901	85	36	12	1826	4	2763	101

Note: Serious non-fatal adverse events include otherwise medically important conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.
*Note that upon manual review of narratives for individual reports, additional information was obtained on age (please see section 6.2.1).

6.2.1 Deaths

There were 48 death reports. During manual review of narratives for individual reports, additional information was obtained on age and it was ascertained that there were 2 pediatric deaths, 38 adult deaths and age was unknown for the remaining 8 deaths.

Pediatric death report: The FAERS received 2 death reports in pediatric Cuvitru recipients during the reporting period. These 2 reports are summarized in Table 3.

Table 3: Pediatric Case Reports with a Fatal Outcome Received in FAERS during Reporting Period

Age (years)	Sex	Indication	Country	Interval	Cause of Death/PTs
12	Female	Immunodeficiency common variable	Foreign	unknown	Unknown*
15	Female	Immunodeficiency common variable	USA	unknown	Unknown**

*Sponsor made 3 follow-up attempts but was unable to obtain additional information.
**The reporter declined consent to be contacted for additional information.

Reviewer comments: Lack of clinical information in the two pediatric death reports precludes further assessment of causal association (in both cases concomitant medications, preceding illnesses, time to onset between treatment and death, and clinical details and circumstances of deaths, were not reported.) In response to an information request, the sponsor confirmed that no further follow-up information was available for these cases. Both patients had a history of common variable immunodeficiency (CVID). CVID is a heterogeneous group of disorders, characterized by hypogammaglobulinemia, defective specific-antibody production.

Primary immunodeficiency diseases are rare yet life-threatening chronic conditions and patients are at increased risk for recurrent bacterial and viral infections. A retrospective

cohort analysis of 26,794 pediatric patients hospitalized with a diagnosis of a primary immunodeficiency diseases from 2003 to 2012 reported overall mortality as 1.99%.[2] In a 2007 study, survival in CVID patients over 20 years was estimated as 64% for males and 67% for females.[3] In a 2019 retrospective review of the largest single-institution cohort of pediatric-onset CVID patients, 9% of patients died within 11 years of diagnosis.[4] Given the underlying relative incidence of mortality in patients with CVID, 2 reports of death in CVID patients using Cuvitru are not unexpected and do not suggest a safety concern.

Adult death reports: The FAERS received 38 death reports in adult recipients (including one duplicate report) and 8 death reports in recipients with unknown age during the reporting period. There were 24 death reports in patients aged 51 to 81 years where the cause of death/preferred terms (PTs) were unknown. The remaining 21 reports are summarized in Table 4.

Table 4: Adult Case Reports with a Fatal Outcome Received in FAERS during Reporting Period

Age (years)	Sex	Indication	Country	Interval	Cause of Death/PTs
35	Female	Common variable immunodeficiency	USA	3 days	Ketoacidosis
Null	Female	Product used for unknown indication	USA	unknown	Sepsis
48	Female	Immunodeficiency common variable	USA	during infusion	Cardio-respiratory arrest
19	Male	Still's disease	Foreign	unknown	Drug ineffective
80	Male	Secondary immunodeficiency	Foreign	44 days	Respiratory failure
68	Female	Product used for unknown indication	Foreign	50 days	Lung neoplasm malignant
81	Female	Immunodeficiency common variable	USA	70 days	Pneumonia
70	Female	Immunodeficiency common variable	USA	84 days	Encephalitis
77	Male	Immunodeficiency	Foreign	17 months	Circulatory collapse, Neoplasm malignant
81	Female	Immunodeficiency common variable	Foreign	5 months	Chronic obstructive pulmonary disease
73	Female	Immunodeficiency common variable	USA	unknown	Ill-defined disorder

[2] Rubin Z, Pappalardo A, Schwartz A, Antoon JW. Prevalence and Outcomes of Primary Immunodeficiency in Hospitalized Children in the United States. J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1705-1710.e1. doi: 10.1016/j.jaip.2017.12.002. Epub 2018 Jan 12. PMID: 29339125.

[3] Brandau AG Jr, Gilbert CA. Common variable immunodeficiency: an uncommon disease with high mortality. J Insur Med. 2007;39(2):71-7. PMID: 17941331.

[4]Baloh C, Reddy A, Henson M, Prince K, Buckley R, Lugar P. 30-Year Review of Pediatric- and Adult-Onset CVID: Clinical Correlates and Prognostic Indicators. J Clin Immunol. 2019;39(7):678-687. doi:10.1007/s10875-019-00674-9

88	Male	Primary immunodeficiency syndrome	Foreign	4 months	Cerebrovascular accident
23	Female	Product used for unknown indication	Foreign	unknown	Respiratory arrest
58	Male	Immunodeficiency common variable	USA	76 days	Myocardial infarction
77	Male	Immunodeficiency common variable	USA	12 months	Pneumonia
78	Female	Immunodeficiency common variable	USA	28 months	Brain neoplasm
78	Female	Immunodeficiency common variable	USA	48 days	Neoplasm malignant
61	Female	Combined immunodeficiency	USA	18 months	Neoplasm malignant
90	Female	Immunodeficiency common variable	USA	unknown	Cerebrovascular accident
79	Male	Immunodeficiency common variable	USA	16 months	Non-Hodgkin's lymphoma
59	Female	Selective IgG subclass deficiency	USA	27 months	Coma

Reviewer comment: Most reports of death following Cuvitru were related to underlying diseases (confounded by indication) or comorbidities. Substantial number of reports had no detail or minimal clinical information on the cause of death. There was insufficient evidence to attribute any of these deaths to Cuvitru. There were no new safety concerns from review of deaths.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 986 serious non-fatal reports; 28 of which involved pediatric patients.

The most frequently reported MedDRA preferred terms (PTs), occurring with a frequency ≥ 2 reports, for serious non-fatal AEs among pediatric patients are summarized in Table 5. (Note that a report may have one or more PTs.)

Table 5: Top PTs for serious non-fatal reports in pediatric patients

Preferred Term (PT)	Number of reports	Label status
Headache	4	Labeled (6.1)
Nausea	4	Labeled (6.1)
Anxiety	3	Unlabeled*
Pneumonia	3	Labeled (14)
Anger	2	Unlabeled*
Asthma	2	Unlabeled**
Chills	2	Unlabeled**
Dyspnoea	2	Labeled (6.2)
Flushing	2	Unlabeled*

Infusion site pain	2	Labeled (6.1)
Paraesthesia oral	2	Unlabeled*
Pyrexia	2	Unlabeled**
Urticaria	2	Unlabeled*

* Unlabeled PT is a non-specific event
** Unlabeled, but related to infection and therefore confounded by indication
6.1 Clinical Trials Experience; 6.2 Postmarketing Experience; 14 Clinical Studies

There were 280 serious non-fatal reports in adults. The most frequently reported PTs, occurring with a frequency ≥ 10 reports, for serious non-fatal AEs among adult patients are summarized in Table 6. (Note that a report may have one or more PTs.)

Table 6: Top PTs for serious non-fatal reports in adult patients

Preferred Term (PT)	Number of reports	Label status
Pneumonia	38	Labeled (14)
Headache	36	Labeled (6.1)
Sinusitis	27	Unlabeled**
Nausea	24	Labeled (6.1)
Fatigue	20	Labeled (6.1)
Urinary tract infection	19	Unlabeled**
Dyspnoea	17	Labeled (6.2)
Pruritus	16	Labeled (6.1)
Bronchitis	15	Unlabeled**
Dizziness	14	Labeled (17)
Infusion site pain	14	Labeled (6.1)
Pyrexia	14	Unlabeled**
Rash	14	Labeled (17)
Urticaria	14	Unlabeled*
Infection	12	Labeled (6.1)
Vomiting	11	Labeled (6.1)
Diarrhoea	10	Labeled (6.1)
Migraine	10	Unlabeled*
Pain	10	Labeled (6.1)

* Unlabeled PT is a non-specific event
** Unlabeled, but related to infection, and therefore confounded by indication
6.1 Clinical Trials Experience; 6.2 Postmarketing Experience; 14 Clinical Studies; 17 Patient Counseling Information

As displayed in above tables, most frequently reported PTs for serious non-fatal reports are either labeled events or non-specific events. There are no new safety concerns.

6.2.3 Non-serious Reports

During the reporting period, there were 1,830 non-serious reports; 37 of which involved pediatric patients. The top ten PTs for non-serious AEs in all ages are shown in Table 7.

Table 7: Top ten PTs for non-serious reports in all ages

Preferred Term (PT)	Number of reports	Label status
Headache	811	Labeled (6.1)
Sinusitis	657	Unlabeled**
Fatigue	549	Labeled (6.1)
No adverse event	526	Not applicable (N/A)
Nausea	421	Labeled (6.1)
Infusion site pain	378	Labeled (6.1)
Infusion site erythema	368	Labeled (6.1)
Pyrexia	317	Unlabeled**
Infusion site swelling	309	Labeled (6.1)
Rash	301	Labeled (17)

** Unlabeled, but related to infection and therefore confounded by indication
6.1 Clinical Trials Experience; 6.2 Postmarketing Experience; 17 Patient Counseling Information

The most frequently reported PTs in non-serious events are labeled or related to labeled events. Similar PTs were seen in pediatric non-serious reports: most frequently reported events in pediatric reports were *Headache* (N = 35); *Pyrexia* (N = 32) and *Infusion site pain* (N = 30). There are no new safety concerns, as these PTs are either labeled or are non-specific terms that do not suggest new conditions attributable to vaccination. The other PT Terms appearing less frequently in pediatric non-serious reports (i.e., in less than 30 reports) were also review and no patterns suggesting a safety concern was identified. Non-serious reports also included a large number of reports with unknown age (N = 1,526).

6.2.4 Reports for patients of unknown age

During the reporting period, there were 2,232 reports for patients of unknown age. The deaths were previously discussed under section 6.2.1. The remaining reports included 678 non-fatal serious events and 1,526 non-serious events (discussed in sections 6.2.2 and 6.2.3).

FAERS received an increase in the number of spontaneous reports since October 2019, and many of these individual case safety reports (ICSRs) were submitted by the sponsor as "age unknown." In response to an information request (submitted under STN 125596/502), the sponsor provided further analysis for these reports. As per the sponsor, "*…the increase in the cases beginning in October 2019 was primarily driven by reports received from Accredo Health; a Specialty Pharmacy involved in a number of Takeda's patient support programs."* Furthermore, the sponsor notes an influx of new patients in Accredo Health following a 6-month moratorium (December 2018 to May 2019) due to supply constraints (of note, in December 2018, CUVITRU was placed on the FDA CBER drug shortage list and a 6-month moratorium was placed on initiating new patients to patient support programs). Accredo Health works with the sponsor to

administer their patient support program (PSP), and *"provides assistance with insurance coverage…personalized care and guidance to help patients manage their therapy."* In the course of administering PSPs such as this one, Sponsors have frequent contact with patients, and, in doing so, they often learn of medical events that patients are experiencing. As a result of these frequent contact with patients, the sponsor submitted solicited adverse event reports obtained by the Accredo Health PSP, which led to an increase in reporting. The sponsor had misclassified the reports received from Accredo Health as spontaneous reports, and going forward, the sponsor plans to classify such reports as study reports. Per FDA Guidance solicited reports arising from a patient support program should be classified as study reports. The sponsor's analysis showed that, there were no significant manufacturing or quality issues, or changes in product distribution (based on indication), and no new safety concerns were identified.

Review of most frequent PTs, and the sponsor's explanation are reassuring and explain the overall increase in report volume and reports of unknown age since October 2019.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Cuvitru 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 for the data mining analysis [11/08/2020]. 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. 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 preferred terms (PTs) summarized in the tables below, with a disproportional reporting alert.

Most of the PTs with elevated disproportionality scores for Cuvitru appeared among the most frequently reported PTs and are discussed in Section 6.2. These are labeled events consistent with the safety profile for Cuvitru. Additionally, the increase in contacts with patients associated with the Accredo Health PSP may have contributed to disproportional reporting for certain PTs for Cuvitru.

Many PTs with elevated disproportionality scores for Cuvitru are for infections or events related to infections. For Cuvitru, similar to other Immune Globulin products, these PTs are most likely related to the patient's underlying conditions, and thus represent confounding by indication, rather than events actually caused or attributable to the product. That is, these events are more likely to be observed in reports in patients who are treated with immune globulins than they are with other products in FAERS. In addition, the increase in contacts with patients associated with the Accredo Health PSP led to an increase in these reports for Cuvitru, compared to other products.

Infection Related PTs	Number of reports
Bacterial infection	13

Infection Related PTs	Number of reports
Bacterial vaginosis	6
Bronchitis	85
Cellulitis	22
Chills	49
Chronic sinusitis	12
Cystitis	26
Ear infection	71
Eye infection	13
Fungal infection	19
Gastroenteritis viral	13
Gastrointestinal infection	11
Infection	79
Influenza	74
Influenza like illness	47
Kidney infection	24
Localised infection	20
Lymphadenopathy	15
Meningitis	8
Meningitis aseptic	7
Nasopharyngitis	100
Pharyngitis	11
Pharyngitis streptococcal	17
Pneumonia	144
Pyrexia	101
Respiratory tract infection	39
Respiratory tract infection viral	6
Sinusitis	367
Skin infection	19
Staphylococcal infection	16
Streptococcal infection	6
Tooth infection	15
Upper respiratory tract infection	65
Urinary tract infection	119
Viral infection	42

Another group of PTs with elevated disproportionality scores for Cuvitru are for infusion site reactions or events related to infusion site reactions. Most of these reports are non-serious and/or are labeled or related to labeled events (i.e., “infusion site reaction” is

labeled). The PT for *Subcutaneous drug absorption impaired* is unlabeled, but may be related to the labeled event "local infusion-site reactions." Disproportional reporting for infusion site reactions for a subcutaneously administered product, compared to intra-venous or intramuscular products for example, is expected.

Infusion Site Related PTs	Number of reports
Infusion related reaction	42
Infusion site bruising	29
Infusion site discolouration	5
Infusion site discomfort	11
Infusion site erythema	92
Infusion site extravasation	71
Infusion site hemorrhage	56
Infusion site induration	10
Infusion site inflammation	4
Infusion site irritation	9
Infusion site mass	16
Infusion site nodule	11
Infusion site pain	130
Infusion site pruritus	48
Infusion site rash	21
Infusion site reaction	28
Infusion site scar	4
Infusion site swelling	98
Infusion site urticaria	7
Infusion site vesicles	5
Infusion site warmth	15
Injection site erythema	42
Injection site extravasation	18
Injection site swelling	34
Subcutaneous drug absorption impaired	6

Remaining PTs were related to known effects of the immune globulin product class or non-specific events. Several other PTs with elevated disproportionality scores are related to labeled or known effects that are common within the immune globulin product class (i.e., Headache, migraine, urticaria). The PTs "Non-specific reaction", "multimorbidity", and "tenderness", are non-specific terms and were observed in relatively few reports. Other PTs with elevated disproportionality scores included "Blood Immunoglobulin G decreased", which is related to the indication for Cuvitru and doesn't represent an adverse effect; "Abdominal distention", which is a non-specific event; "Contact dermatitis", which could be caused by an allergy and were observed in

relatively few reports; "Incorrect drug administration rate" and "liquid product physical issue" are administration/product issue not related to any safety concerns.

Other PTs	Number of reports
Abdominal distension	38
Blood immunoglobulin G decreased	6
Dermatitis contact	9
Device infusion issue	5
Headache	254
Incorrect drug administration rate	22
Liquid product physical issue	8
Migraine	49
Multimorbidity	4
Nonspecific reaction	7
Swelling	53
Tenderness	8
Urticaria	59

There are no new safety concerns from review of data mining results.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Cuvitru covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in the 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 U.S. National Library of Medicine's PubMed.gov database on November 12, 2020 , for peer-reviewed literature, with the search term "Cuvitru" and published dates between September 13, 2016 and September 30, 2020 retrieved 4 articles. Titles and abstracts were reviewed for relevance to safety information for Cuvitru, and one article relevant to safety for Cuvitru was identified and is summarized in Table 8. No new safety concerns for Cuvitru were identified.

Table 8: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Suez D, Kriván G, Jolles S, et al. Safety and tolerability of subcutaneous immunoglobulin 20% in primary immunodeficiency diseases from two continents. *Immunotherapy*. 2019 Aug;11(12):1057-1065.	This pooled analysis evaluated the safety and tolerability of the subcutaneous immunoglobulin 20% product, Ig20Gly, in primary immunodeficiency diseases using data from two Phase II/III studies conducted in North America and Europe. The study concluded that Ig20Gly was well tolerated in a broad population of patients with primary immunodeficiency diseases.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Cuvitru does not indicate any new safety concerns. The PAC review was initiated due to approval of Cuvitru for the treatment of primary humoral immunodeficiency in adult and pediatric patients two years of age and older on September 13, 2016. 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 Cuvitru.