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)
From:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Octapharma
Product:	Panzyga, immune globulin (human)-ifas 10%
STN:	125587/176
Indication:	Indicated for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older; chronic immune thrombocytopenic purpura (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP) in adults
Meeting Date:	Pediatric Advisory Committee Meeting, April 2022

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 August 2, 2018 approval of Panzyga for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older.
(Note that the August 2, 2018 approval also includes the indication for the treatment of chronic immune thrombocytopenic purpura (ITP) in adults.)

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

Panzyga [immune globulin (human)-ifas 10%] is an intravenous human immunoglobulin solution with a protein content of 10%. Panzyga is derived from large pools of human plasma. The manufacturing process achieves viral reduction through a combination of two steps: solvent/detergent (S/D) treatment and nanofiltration with a 20 nm filter. All units of human plasma used in the manufacture of Panzyga are provided by FDA approved blood and plasma establishments and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV1 and found to be non-reactive (negative).

1.3 Regulatory History

- August 2, 2018 approval of original BLA 125587/0 for the treatment of PI in patients ≥ 2 years* and ITP in adults.
  **Trigger for the PAC*
- February 11, 2021 approval of sBLA 125587/70 for a new indication for the treatment of adults ≥ 18 years with chronic inflammatory demyelinating polyneuropathy (CIDP).

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
  - FAERS reports for Panzyga during August 2, 2018 to October 22, 2021
- Manufacturer's Submissions
  - Panzyga, U.S. package insert (USPI), updated March 24, 2021
  - Applicant response to information request regarding dose distribution data
  - Applicant response to information request dated November 3, 2021 regarding update pharmacovigilance plan (PVP)

    - Risk Management Plan (RMP), version 4.1, dated March 15, 2021
    - Periodic safety reports
- FDA Documents
    - BLA 125587/0 Panzyga Approval Letter, dated August 2, 2018
    - BLA 125587/0 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]

For the time period of August 2, 2018 to October 22, 2021, there were (b) (4) of Panzyga distributed in U.S. For the time period of August 2, 2018 to October 22, 2021, there were 14,014, 367g of Panzyga distributed worldwide. The sponsor is not able to provide additional information on patient exposure in the pediatric age group (< 18 years) versus adults (≥18 years).

Using the U.S. distribution data above, a rough estimate of doses would be (b) (4) doses. (Since dose is based upon weight, indication, and clinical response, the above figure is only a general estimate. 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, and the dosage administered. Additionally, the package insert notes that significant differences in the half-life of IgG among patients with PI may necessitate the dose and frequency of immunoglobulin therapy to vary from patient to patient.)

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP) is the Risk Management Plan (RMP), version 4.1, dated March 15, 2021, which lists the important identified risks, important potential risks, and missing information displayed in Table 1.

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

Table 1: Panzyga safety concerns

Important Identified Risks
• Thromboembolic events • Aseptic meningitis • Hypersensitivity reactions, including anaphylactic reactions • Acute renal failure • Hemolysis
Important Potential Risks
• Transmission of infectious agents • Interaction with live attenuated virus vaccines and serological testing • Transfusion-related acute lung injury (TRALI) • Neutropenia/leukopenia
Missing Information
• Safety in elderly patients • Safety in pregnant or breastfeeding women • Safety in patients with renal or hepatic impairment

The identified and potential risks for Panzyga listed in the above table are common to the immune globulin product class, and most of these risks are described in the USPI. Panzyga has a boxed warning for thrombosis, renal dysfunction and acute renal failure. The USPI includes Warnings for thrombotic events, aseptic meningitis syndrome, hypersensitivity, renal failure, hemolysis, TRALI, transmission of infectious agents. Interaction with live attenuated virus vaccines and serological testing is described in section 7 *Drug Interactions* of the USPI. Neutropenia/leukopenia has been reported after immune globulin treatment and may be attributed to antineutrophil antibodies present in the immune globulin.

Thrombotic events: Prior to this PAC trigger, in 2013, a boxed warning[2] for thrombosis was added to the label of all non-specific immune globulin products, as required by FDA. As per FDA safety communication, "A retrospective analysis of data from a large health claims-related database, as well as continued postmarketing adverse event reports of thrombosis, have strengthened the evidence for an association between the use of intravenous, subcutaneous, and intramuscular human immune globulin products and the risk of thrombosis. This information necessitates a boxed warning for the entire class of products."[3] The risk of thrombosis was identified prior to the approval for Panzyga, and it is considered applicable to all immune globulin products and labeled for this entire product class.

[2] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. November 7, 2013. Available at: https://www.gmp-compliance.org/gmp-news/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

[3] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. June 11, 2013. Available at: https://primaryimmune.org/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

The identified and potential risks for Panzyga 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 for Panzyga, such as postmarketing safety studies or Risk Evaluation and Mitigation Strategy (REMS).

5.2 Postmarketing studies

There are no safety-related postmarketing requirement or commitment (PMR/PMC) studies for Panzyga.

Studies under the Pediatric Research Equity Act (PREA) are listed below:

- Deferred pediatric study under PREA for the treatment of ITP will evaluate efficacy and safety of Panzyga in patients ages ≥ 1 year to < 18 years.
  Final Protocol Submission: June 30, 2019
  Study Completion Date: April 30, 2022
  Final Report Submission: October 31, 2022
- Deferred pediatric study under PREA for the treatment of CIDP in pediatric patients ages 2 to 17 years of age.
  Final Protocol Submission: June 30, 2021
  Study Completion Date: June 30, 2025
  Final Report Submission: December 31, 2025

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Panzyga received between August 2, 2018 (PAC trigger) to October 22, 2021 (data lock point for this review period). 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 Panzyga during the review period are listed in Table 2. There were 56 U.S. and 59 foreign reports.

Table 2: FAERS reports for Panzyga (August 2, 2018 to October 22, 2021)

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	2*	5	0	1	1	0	3	6
≥18	30	45	1	5**	9	1	40	51
Unknown	2	2	0	0	11	0	13	2
All	34	52	1	6	21	1	56	59

*One unique case.

** Includes one duplicate case.

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).

6.2.1 Deaths

There were 7 death reports representing 6 unique cases, including 1 pediatric death. These reports are summarized below. There were no new safety concerns from review of deaths.

Pediatric death (foreign report): 13-year-old male with rare mitochondrial disease MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes) syndrome and complicated past medical history that included, bronchopulmonary dysplasia, chronic pneumonitis, gastrostomy was admitted to a hospital for pneumonia and experienced worsening dyspnea, fever, and deteriorating clinical course. Acute respiratory distress syndrome, encephalopathy and multiple organ dysfunction syndrome were reported as causes of death.

Reviewer comments: The death was related to the patient's underlying disease and comorbidities and is not attributed to Panzyga.

Adult deaths:

- 64-year-old woman with Hodgkin´s lymphoma, neutropenia, and peritoneal carcinomatosis and multiple comorbidities experienced intense back pain and abdominal pain following Panzyga. The patient died due to relapsing lymphoma with peritoneal carcinomatosis and intestinal obstruction.

- 67-year-old woman with relapsing follicular non-Hodgkin's lymphoma, venous thrombosis, neuropathy syndrome and multiple comorbidities received Panzyga and developed fever, dyspnea, tachycardia and nausea. Neuropathy syndrome continued to progress with motor impairment of limbs and diaphragm and the

patient died.

- 82-year-old man with Guillain-Barre syndrome and past medical history that included hypertension, prostate neoplasm, lymphoma, received Panzyga and developed fever, chills, hypertension and hypoxia. Additional follow-up information indicated that he had developed cytomegalovirus positive colitis which progressed to toxic megacolon and fatal sepsis.

- 76-year-old woman with non-Hodgkin lymphoma and cytopenia and multiple comorbidities received Panzyga and developed chills, fever and tachycardia and hemolysis. Additional follow-up information was obtained indicating that the patient had died due to lymphoma.

- 55-year-old man with Guillain-Barre syndrome and who was wheelchair bound, received Panzyga. As per report, “the patient had a seizure, was hospitalized and found to have blood clots and ultimately had a heart attack and passed away.” No additional clinical information is provided.

Reviewer comments: The reports of death following Panzyga were related to underlying diseases or comorbidities, or contained too little clinical information for attribution to the product. There was insufficient evidence to attribute any of these deaths to Panzyga.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 86 serious non-fatal reports; of which 7 reports involved pediatric patients. The pediatric reports included 2 US reports representing one unique case and 5 foreign reports. The six pediatric cases are summarized below.

- 13-year-old male presented with headaches, photophobia, odor sensitivity and was treated with Panzyga for encephalopathy. He had received prior treatment with Gammagard. Headaches lasted 1-2 weeks and patient recovered.

- 9-year-old female presented with Kawasaki’s disease and was treated with Panzyga and developed hemolysis secondary to administration of immunoglobulin.

- 7-year-old male with acute lymphocytic leukemia received Panzyga and developed stridor, high temperature, fall in blood pressure and maculopapular rash.

- 15-year-old female with type 2 diabetes, developed septic shock secondary to left elbow cellulitis and immunosuppression

- 3-year-old male with acute lymphocytic leukemia and disseminated candidiasis experienced fever, chills, tachypnea, tachycardia and abdominal pain with a drop

in hemoglobin indicating a hemolytic reaction. He received blood transfusions and outcome was reported as recovered.

- 13-year-old male received Panzyga for treatment of common variable immunodeficiency, and experienced headache, fever, chills, nausea, and aseptic meningitis. He received diphenhydramine and hydrocortisone and outcome was reported as recovered.

The most frequently reported PTs occurring in >10 serious reports are shown in the table below. Note that a report may have one or more PTs.

Table 3: Top PTs for serious reports

Preferred Term (PT)	Number of reports	Label status
Chills	31	Labeled (6.1 Clinical Trials Experience)
Dyspnoea	26	Labeled (6.2 Postmarketing Experience)
Tachycardia	21	Labeled (6.2 Postmarketing Experience)
Headache	19	Labeled (6.1 Clinical Trials Experience)
Tachypnoea	19	Unlabeled
Pyrexia	18	*Fever* is labeled (6.1 Clinical Trials Experience)
Hypertension	17	Labeled (5.8 Warnings; 6.2 Postmarketing Experience)
Febrile nonhaemolytic transfusion reaction	13	Unlabeled
Nausea	11	Labeled (6.1 Clinical Trials Experience)

Panzyga, USPI, updated March 24, 2021

As displayed in Table 3, most frequently reported PTs for serious reports are labeled events or related to labeled events. The unlabeled PT for *Tachypnea* is a non-specific event that may occur with other related labeled events. The PT for *Febrile nonhaemolytic transfusion reaction* is related to the labeled event *Infusion reaction* (6.1 Clinical Trials Experience). No new safety concerns were identified.

6.2.3 Non-serious Reports

During the reporting period, there were 22 non-serious reports; of which 1 report involved a pediatric patient. The pediatric report involved a 16-year-old male with reported PTs for *Panic Attack, Dyspnea, Dysphagia, Infusion related reaction*. The most frequently reported PTs occurring in > 2 non-serious reports are shown in Table 4. Note that a report may have one or more PTs.

Table 4: Top PTs for non-serious reports

Preferred Term (PT)	Number of reports	Label status
Urticaria	6	Labeled (6.2 Postmarketing Experience; 17 Patient Counseling Information)
Pruritus	6	Labeled (6.2 Postmarketing Experience)
Nausea	5	Labeled (6.1 Clinical Trials Experience)
Rash	5	Labeled (6.2 Postmarketing Experience)
Headache	4	Labeled (6.1 Clinical Trials Experience)
Dyspnoea	3	Labeled (6.2 Postmarketing Experience)
Infusion related reaction	3	*Infusion reaction* is labeled (6.1 Clinical Trials Experience)

Panzyga, USPI, updated March 24, 2021

The most frequently occurring PTs in non-serious reports are labeled.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Panzyga 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 as of October 29, 2021. 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 PTs summarized in the table below, with a disproportional reporting alert. Note that a report may have one or more PTs.

Preferred Term (PT)	Label status
Acute pulmonary oedema	*Noncardiogenic pulmonary edema* labeled (5.7 Warnings)
Anti A antibody positive	Unlabeled*
Blood pressure increased	Labeled (6.1 Clinical Trials Experience)
Chest pain	Labeled (6.2 Postmarketing Experience; 17 Patient Counseling Information)
Chills	Labeled (6.1 Clinical Trials Experience)
Cyanosis	Labeled (6.2 Postmarketing Experience)
Dyspnoea	Labeled (6.2 Postmarketing Experience)
Febrile nonhaemolytic transfusion reaction	Unlabeled
Feeling cold	Labeled (6.2 Postmarketing Experience)

Preferred Term (PT)	Label status
Haemolysis	Labeled (5.6 Warnings; 6.2 Postmarketing Experience; 17 Patient Counseling Information)
Headache	Labeled (6.1 Clinical Trials Experience)
Hepatitis B core antibody positive	Unlabeled*
Hepatitis B surface antibody positive	Unlabeled*
Hypertension	Labeled (5.8 Warnings; 6.2 Postmarketing Experience)
Infusion related reaction	*Infusion reaction* is labeled (6.1 Clinical Trials Experience)
Meningitis aseptic	*Aseptic meningitis syndrome* is labeled (5.5 Warnings; 17 Patient Counseling Information)
Nausea	Labeled (6.1 Clinical Trials Experience)
Pyrexia	*Fever* is labeled (6.1 Clinical Trials Experience)
Tachycardia	Labeled (6.2 Postmarketing Experience)
Tachypnoea	Unlabeled
Tremor	Labeled (6.2 Postmarketing Experience)
Urticaria	Labeled (6.2 Postmarketing Experience; 17 Patient Counseling Information)
Wheezing	Labeled (6.2 Postmarketing Experience; 17 Patient Counseling Information)

*Not adverse events.
Panzyga, USPI, updated March 24, 2021

Most of the above PTs are labeled or related to labeled events, and were previously seen among the most frequently reported PTs for serious and non-serious adverse events. The following PTs are not adverse events, and represent results of laboratory testing: Anti A antibody positive; Hepatitis B core antibody positive; Hepatitis B surface antibody positive. IgA-deficient patients have antibodies against IgA. The reports of positive serology for Hepatitis B were foreign reports with limited information to assess a causal relationship. Of note, the manufacturing process for Panzyga achieves viral reduction through solvent/detergent treatment and nanofiltration.

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 Panzyga covering the surveillance period were reviewed. The adverse events 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 U.S. National Library of Medicine's PubMed.gov database on November 15, 2021, for peer-reviewed literature, with the search term "Panzyga" and

published dates between August 2, 2018 and November 15, 2021, retrieved 2 articles. Titles and abstracts were reviewed for relevance to safety information and is summarized below. No new safety concerns were identified.

Table 5: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Arbach O, Taumberger AB, Wietek S, Cervinek L, Salama A. Efficacy and safety of a new intravenous immunoglobulin (Panzyga®) in chronic immune thrombocytopenia. Transfus Med. 2019 Feb;29(1):48-54. doi: 10.1111/tme.12573. Epub 2019 Jan 27. PMID: 30687970; PMCID: PMC6850321.	Presents the data from the prospective, open-label, non-controlled phase 3 study of Panzyga (intravenous immunoglobulin (IVIG) 10%) in patients with chronic immune thrombocytopenia (ITP). Full analysis set comprised of 36 patients. Adverse events were mainly mild to moderate in severity, and the most frequent was headache. The authors conclude that Panzyga is well tolerated even at a high infusion speed.
Ochs HD, Melamed I, Borte M, Moy JN, Pyringer B, D Kobayashi AL, Knutsen AP, Smits W, Pituch-Noworolska A, Kobayashi RH. Intravenous immunoglobulin 10% in children with primary immunodeficiency diseases. Immunotherapy. 2018 Oct;10(14):1193-1202. doi: 10.2217/imt-2018-0074. Epub 2018 Aug 8. PMID: 30088423.	Presents data from two prospective, open-label and noncontrolled multicenter phase 3 studies of Panzyga in 25 patients <16 years of age with primary immunodeficiency disease. Abdominal pain, headache and chills were the most common treatment-related adverse events. The authors conclude that Panzyga is safe and effective for the treatment of predominantly antibody-deficient children.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Panzyga does not indicate any new safety concerns. The PAC review was initiated due to approval of Panzyga for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older on August 2, 2018. In general, there were few pediatric reports during this review period. 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 Panzyga.