



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

MEMORANDUM

Date: 3 July 2018

From: Wambui Chege, MD
Medical Officer, Pharmacovigilance Branch

Re: STN 125587/0.45

Through: Adamma Mba-Jonas, MD
Branch Chief, Pharmacovigilance Branch

Scott Proestel, MD
Director, Division of Epidemiology

Product: Panzyga (Immune Globulin Intravenous Human 10%)

Proposed indication: For the treatment of:

- Primary humoral immunodeficiency (PI)
- Chronic immune thrombocytopenia (ITP) in adults

Submission: Sponsor Response to FDA Complete Response Letter

Sponsor: Octapharma

ADD: 2 August 2018

1. INTRODUCTION

Panzyga is a human immune globulin (IG) produced by Octapharma. The product is available as a 10% liquid for intravenous (IV) administration. In development, the product was called NewGam 10%. For purposes of clarity in this memorandum, the product will be referred to as Panzyga, the proposed U.S. trade name.

On 15Apr2015, Octapharma submitted an original Biologics License Application (BLA, 125587/0) to the Food and Drug Administration (FDA) for Panzyga. Following review of the original BLA, FDA issued a Complete Response (CR) letter to Octapharma on 10Feb2016. Deficiencies outlined in the CR letter included an inspectional issue, a clinical pharmacology issue, a labeling issue and 17 review issues. The review issues included concerns regarding sterility at sponsor facilities, validation reports regarding the manufacturing process and excipients, as well as container closure integrity and the risk of (b) (4).

At the time of review of the original BLA, an assessment of the clinical safety and efficacy data submitted by the sponsor was conducted by the Division of Hematology Research and Review in FDA's Office of Blood Research and Review (DHRR/OBRR).¹ This review determined that "[t]he safety profile of Panzyga is similar to that of other products in this class" and ultimately concluded that "[c]ompared with other members of the product class Panzyga is safe and effective for the conditions studied." In addition, the memorandum recommended approval for the indication of primary immunodeficiency (PI) in adults and children aged ≥ 2 years and for the indication of chronic idiopathic thrombocytopenic purpura (ITP) in adults. It was further recommended that FDA require the sponsor to conduct a postmarketing study (PMR) "in pediatric subjects with ITP where the study enrolls a population reflecting U.S. demographics characteristics."

In addition to providing clinical data at the time of submission of the original BLA, the sponsor also provided a Pharmacovigilance Plan (PVP).² The PVP was reviewed in detail by FDA's Division of Epidemiology (DE) in the Office of Biostatistics and Epidemiology (OBE). The review by DE/OBE concluded that "should the product be licensed, routine pharmacovigilance is recommended to monitor the risks associated with Panzyga" and further noted that the "available data do not suggest a safety signal that would trigger either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint."³ Neither the clinical review by DHRR/OBRR, nor the PVP review by DE/OBE identified any deficiencies that contributed to the CR letter.

2. OBJECTIVE

On 31Jan2018, Octapharma submitted a response to FDA's CR letter (125587/0.45), addressing the deficiencies identified by FDA during review of the original BLA. The purpose of this memorandum is to evaluate any available interim clinical safety data identified since review of the original BLA, and assess the adequacy of the proposed PVP.

¹ FDA. LandowL Clinical Review. Panzyga. 5Jan2016 eCTD 125587/0

² Octapharma. Risk Management Plan No 01. Panzyga. 23Mar2015 eCTD 125587/0

³ FDA. PaulW Pharmacovigilance Plan Review. Panzyga. 15Jan2016 eCTD 125587/0

3. INTERIM SAFETY DATA

a. FDA Adverse Event Reporting System

A search of the FDA Adverse Event Reporting System (FAERS) on 3Jul2018 for any reports submitted listing the trade name Panzyga with no additional search restrictions yielded a single report – FAERS report 13735140. Data mining was deferred due to the small number of reports in the database.

The single FAERS report retrieved by the search was received by Octapharma from a health care professional in Canada and describes a 79-year-old female patient with chronic lymphocytic leukemia. On (b) (6), her hepatitis B virus surface antigen and hepatitis B virus core total antibody were not reactive. The patient received treatment for prophylaxis of secondary hypogammaglobulinemia with Octagam 10% on (b) (6). She was then switched to Panzyga, which was administered monthly from (b) (6). On (b) (6), the patient was tested for hepatitis B virus core antibody and was reactive. Hepatitis B virus surface antibody was 461 IU/L and hepatitis B virus surface antigen was still non-reactive. The report further describes internal analysis of batch quality review on 17Jul2017 by the sponsor, in which a quality review of the manufacturing process and final testing of the concerned Octagam 10% and Panzyga batches did not reveal any observations, deviations or irregularities that could have had a negative impact on the quality of the product. Octapharma reports that all final product specification tests fulfilled the acceptance criteria at the time of release.

b. International Postmarketing Data

Octapharma reports that Panzyga was first approved in Germany on 15Feb2016 and that as of 19May2018 the product is approved in a total of 30 countries including Canada and multiple European countries.⁴ The sponsor has submitted a total of 9 Periodic Safety Update Reports (PSUR) describing the international postmarketing experience over a period of about 3 years from 04Jun2015 to 19May2018. The most recent PSUR submitted by the sponsor provides both interval and cumulative data regarding the international postmarketing experience with Panzyga and has been reviewed in detail. The Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) each reported more than 10 times on spontaneous Individual Case Safety Reports (ICSRs) received by the sponsor for Panzyga during the cumulative time period (i.e. 15Feb2016 to 19May2018) are listed in Table 1 below. The sponsor defines spontaneous reports as those received from health authorities, consumers and the literature but excluding reports from non-interventional postmarketing studies. These PTs were consistent with hypersensitivity/infusion reactions, and of those reported, the most common were chills and headache.

⁴ Octapharma. Periodic Safety Update Report No. 9 eCTD 125587/5

Table 1. Most frequent PTs for all adverse event reports received by Octapharma for Panzyga from 15Feb2016 to 19May2018.⁵

MedDRA Preferred Term	(n)
Chills	39
Headache	39
Blood pressure increased	31
Nausea	27
Back pain	17
Dyspnoea	17
Erythema	17
Hypertension	15
Vomiting	14
Pruritus	13
Pyrexia	13
Urticaria	12

An overview of serious ICSRs received by the sponsor for Panzyga in both the cumulative and interval periods are listed in Table 2 below.

Table 2. Overview of Serious ICSRs received by Octapharma for Panzyga⁶

Product	Total no. of ICSRs	Total no. of serious ICSRs	Serious/Total ICSRs (%)
Cumulative period (IBD to 19-May-2018)			
Panzyga	154	54	35%
Generic IVIG	8	5	63%
Generic IG	2	2	100%
Interval period (20-Jan-2018 to 19-May-2018)			
Panzyga	72	21	29%
Generic IVIG	5	3	60%
Generic IG	0	0	-

ICSR = Individual Case Safety Reports, IBD = International Birth Day for Panzyga 15Feb2016

The sponsor further reports that none of the serious ICSRs received in the reporting interval resulted in a fatal outcome after receipt of Panzyga. However, one serious ICSR following administration of generic IVIG resulted in death. The sponsor describes this fatal ICSR from a literature report of a patient with ITP who was treated with an IVIG. No brand name or treatment details were provided. The patient failed to respond to three consecutive lines of treatment, had multiple comorbidities and died on an unspecified date due to intracranial haemorrhage. Octapharma assesses this report as unlikely related to IVIG treatment as intracranial

⁵ Adapted from Appendix 2b – Cumulative and interval summary tabulations from post-marketing experience.p.45-51. Octapharma. Periodic Safety Update Report No. 9 eCTD 125587/5

⁶ Adapted from Table 5, p 12. Octapharma. Periodic Safety Update Report No. 9 eCTD 125587/5

haemorrhage is a complication of ITP and thus most likely related to the patient's underlying condition.⁷

Of note, serious adverse event reports in the prelicensure clinical safety data base, including 2 fatal reports, have previously been reviewed by OBE/DE at the time of submission of the original BLA.³ These two reports of death were thought likely to be unrelated to Panzyga.

4. PHARMACOVIGILANCE PLAN

Octapharma reports that as of 19May2018, version 03 of the Risk Management Plan (RMP) for Panzyga dated 26Nov2015 is in effect, and the sponsor has reviewed the safety concerns listed in the RMP which are summarized in Table 3 below.⁴ Octapharma reports that most of the safety concerns are addressed using MedDRA queries to search for defined terms as part of the sponsor's routine pharmacovigilance. The identified cases are medically evaluated by the sponsor to determine whether they are indicative of the respective safety concern.⁴

Table 3. Summary of safety concerns

Important Identified Risks	<ul style="list-style-type: none">- Thromboembolic events- Aseptic meningitis- Hypersensitivity reactions, including anaphylactic reactions- Acute renal failure- Haemolysis
Important Potential Risks	<ul style="list-style-type: none">-Transmission of infectious agents-Interaction with live attenuated virus vaccines and serological testing
Missing Information	<ul style="list-style-type: none">- Safety in elderly patients- Safety in pregnant or breast-feeding women- Safety in patients with renal or hepatic impairment

Compared with the safety concerns described at the time of submission of the original BLA, the sponsor has added one Important Potential Risk – interaction with live attenuated virus vaccines and serological testing. The sponsor notes that the rationale for addition of this safety concern is that administration of an IVIG product “may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines” and that to avoid this risk “an interval of 3 months after administration of this medicinal product should elapse before vaccination with live attenuated virus vaccines.”⁸ Within the reporting interval of the most recent PSUR, no ICSRs with Panzyga as suspect drug were identified that are indicative of an interaction with live attenuated virus vaccines or serological testing.

5. DISCUSSION

This review of the available interim safety data of Panzyga identified a single FAERS report (section 3a above) which appears to describe the passive transfer of antibodies in a patient who was previously seronegative for hepatitis B. The patient remained negative for hepatitis B

⁷ Deplano S, Atta M, Luqmani A *et al.* Immune thrombocytopenia in the elderly: A single centre experience. *BJHEAL* | 2018; 181(Suppl):51.

⁸Octapharma. Periodic Safety Update Report No. 9 p. 28 eCTD 125587/5

surface antigen and testing of the lots of Panzyga by the sponsor were unremarkable, suggesting that the change in the patient's serological markers was due to passive transfer of antibodies rather than active infection following administration of IVIG. The potential for passive transfer of antibodies to confound serological testing in patients receiving IVIG is well-described in the literature and is listed in the proposed package insert for Panzyga.

The most recent international postmarketing safety data for Panzyga has also been reviewed (section 3b above). The PTs listed most frequently on ICSRs received by the sponsor are consistent with hypersensitivity or infusion reactions (Table 1 above). The risk of severe hypersensitivity reactions occurring during infusions of Panzyga is listed in the Warnings and Precautions section of the proposed package insert. The sponsor also reports in the most recent PSUR that about a third of reports received for Panzyga in both the cumulative and interim periods are classified as serious (Table 2 above). This proportion of serious reports is consistent with other products in the class. No deaths following administration of Panzyga were reported in the most recent PSUR and the single fatal report after a generic IVIG cannot be attributed to the product given the patient's comorbidities and underlying conditions. In summary, review of the available interim safety data for Panzyga has not identified any new safety concerns.

The sponsor provides a reasonable rationale for the addition to the PVP of a new Important Potential Risk – interaction with live attenuated virus vaccines and serological testing (section 4 above). The proposed label for Panzyga includes a statement that “administration of live viral vaccines, if indicated can be appropriately delayed for 3 or more months from the time of Panzyga administration.”⁹

6. RECOMMENDATION

As noted in the previous DE/OBE PVP review, the available data do not indicate a safety signal that would trigger a REMS, PMC or PMR that is specifically designed to evaluate safety as a primary endpoint. Should the product be licensed, routine pharmacovigilance as described in the PVP is recommended to monitor the risks associated with Panzyga. Updates to the PVP will be reviewed when available. In addition, OBE/DE will participate in labeling discussions to bring the pregnancy section of the package insert into compliance with FDA's Pregnancy and Lactation Labeling Rule.

⁹ Octapharma. Draft labeling. eCTD 125587/0.45