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

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

To:	Adriane Fisher, MPH, MBA Office of Tissues and Advanced Therapies
Through:	Adamma Mba-Jonas, MD, MPH Chief, Pharmacovigilance Branch (PVB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER) Meghna Alimchandani, MD Deputy Director, DE, OBE, CBER
From:	Bethany Baer, MD Medical Officer, PVB, DE, OBE, CBER
Subject:	Review of the Pharmacovigilance Plan for efficacy supplement
Applicant:	Octapharma
Product:	Octagam 10% [Immune Globulin Intravenous (Human)]
Submission STN:	125062/674
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Adamma C. Mba-jonas -S
Digitally signed by Adamma C. Mba-jonas -S
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Bethany M. Baer -S
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1 OBJECTIVE

This memorandum is in response to a request from the Office of Tissues and Advanced Therapies (OTAT) to the Division of Epidemiology (DE) to review the Pharmacovigilance Plan for the Octagam 10% efficacy supplement to add the indication of dermatomyositis.

2 INTRODUCTION

A. Background

Immune globulins derived from donated human plasma have been used for decades and are prescribed for the treatment of a wide range of conditions including immunodeficiencies, neurologic disorders, and autoimmune/inflammatory disorders. Many immune globulin products are approved to treat primary immunodeficiency while several products are approved for additional indications. There is also widespread use for conditions not listed in a product's indication. A recent review found that in the US, neurological conditions including chronic inflammatory demyelinating polyneuropathy accounted for 41% of immune globulin use by grams. Allergy and immunology indications, including primary immunodeficiencies, accounted for 28% of usage. Hematology and oncology disorders, including chronic idiopathic thrombocytopenic purpura, accounted for 16% of usage.[1]

Dermatomyositis is an idiopathic inflammatory myopathy and a rare disease with an incidence of approximately 1/100,000 persons.[2] In addition to inflammation of the striated muscles that causes proximal muscle weakness, patients can have gastrointestinal, pulmonary, and cardiac involvement. Patients with dermatomyositis are at increased risk of multi-organ disease. Patients with dermatomyositis are also at an increased risk of thromboembolic events. One study of venous thromboembolic events with polymyositis and dermatomyositis showed incidence rate ratios of 6.77-9.66 for dermatomyositis patients.[3] A meta-analysis of 6 studies including over 9,000 patients with polymyositis or dermatomyositis showed a pooled odds ratio of 4.31 (95% CI:2.55-7.29) for venous thromboembolism in all inflammatory myositis and an odds ratio of 11.59 (95% CI: 6.54-20.55) for dermatomyositis specifically.[4]

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[1] Robert P, Hotchko M. Polyvalent immune globulin usage by indication in the United States, 2012: a quantitative analysis of the use of polyvalent immune globulin (intravenous and subcutaneous) by medical indication in the United States in 2012. Transfusion.2015 Jul;55 Suppl 2:S6-12.

[2] Bendewald MJ, Wetter DA, Li X, et al. Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study of Olmsted County, Minnesota. Arch Dermatol. 2010;146(1):26.

[3] Carruthers EC, Choi, HK, Sayre EC, et al. Risk of Deep Venous Thrombosis and Pulmonary Embolism in Individuals with Polymyositis and Dermatomyositis: A General Population-Based Study. Ann Rheum Dis. 2016;75(1):110-6.

[4] Li Y, Wang, P, Li L, et al. Increased risk of venous thromboembolism associated with polymyositis and dermatomyositis: a meta-analysis. Therapeutics and Clinical Risk Management. 2018:14:157-65.

B. Product Information

Octagam is an intravenous immune globulin (human). It is available as a 5% liquid indicated for treatment of primary humoral immunodeficiency (PI). A 10% liquid version of Octagam is also licensed in the US and is indicated for treatment of chronic immune thrombocytopenic purpura (ITP). The Octagam 10% dose for ITP is 2g/kg, divided into two daily doses of 1 g/kg given on 2 consecutive days.

C. Regulatory History

Octagam was initially licensed in the US as a 5% version in 2004. It was voluntarily withdrawn from the US market in August 2010 in response to an increased number of spontaneous adverse event reports of thromboembolism associated with its use. High levels of factor XIa were found to be the putative cause of this increased reporting of thromboembolic events (TEEs). Manufacturing changes were made to reduce levels of factor XIa in Octagam. Octagam was re-introduced to the US market in Nov. 2011. A safety postmarketing requirement (PMR) study did not identify an increased risk of TEEs after Octagam 5% compared to other US-licensed intravenous immune globulin (IVIG) products (please see section 5). Octagam 10% was licensed in 2014.

3 MATERIALS REVIEWED

Source	Subtype	Document Reviewed
Octapharma	125062/674	Risk Management Plan, Version 11.1 including US Specific Addendum, Nov. 4, 2020
Octapharma	125062/674	Clinical Overview, Sept. 2020
Octapharma	125062/674	Summary of Clinical Safety, Sept. 2020
Octapharma	125062/674	Clinical Study Report for Study GAM10-08
Octapharma	125062/674/5	Risk Management Plan, Version 11.2, including US Specific Addendum, Mar. 8, 2021
Octapharma	125062/674/6	Response to Feb. 24, 2021 Information Request on Labeling
Octapharma	125062/674/8	Response to May 18, 2021 Information Request; Risk Management Plan, Version 11.2a , including US Specific Addendum, May 26, 2021
Octapharma	125062/674/12	Response to Jun 24, 2021 Information Request on TEE analysis in periodic safety reports
FDA	Memo	FDA Review of Final Study Report for Study GAM5-28, by Bethany Baer, dated Oct. 23, 2020

4 CLINICAL SAFETY DATABASE[5]

A. Clinical Trial Exposure

The Octagam clinical development program has included (b) (4) interventional studies, with (b) (4) of those using Octagam 10%. A total of (b) (4) patients were treated in the clinical trials. Of these, (b) (4) received Octagam 5% and (b) (4) received Octagam 10%. Nearly all of the patients (96.9% of the (b) (4) subjects with known ethnic origin) in the clinical trials were Caucasian. Of note, patients with risk factors for thromboembolic events (TEEs) that were considered to outweigh the potential benefit of Octagam treatment were excluded from the trials. The list of risks included obesity, advanced age, hypertension, diabetes, and a history of vascular disease or thrombosis. (b) (4)

(b) (4)

The two larger, most relevant Octagam 10% studies are presented in Table 1 below:

Table 1: Clinical studies for Octagam 10%

Study Phase	Description	Age	Sample Size
GAM10-02 Phase 3	For the indication of ITP, prospective, open-label, uncontrolled, multicenter	17-88 years old	116 subjects
GAM10-08 Phase 3	For the indication of dermatomyositis, double-blind, randomized, placebo-controlled study with a 6-month open label extension period	22-79 years old	95 subjects

B. Adverse Events from the Clinical Trials

In Study GAM10-02 for the ITP indication, there were 115 patients in the full analysis. Sixty-six had chronic ITP and 49 were newly-diagnosed. The subjects were 64% female and ranged in age from 17-88 years old. They were 100% White. There was a drug-related adverse event (AE) in 55% of subjects. The most common drug-related AEs were headache (29 subjects), fever (17 subjects), and increased heart rate (13 subjects). There was one drug-related serious AE reported. This serious event was a headache. There was a serious AE of a transient ischemic attack that accompanied ITP in a chronic ITP patient. The TIA was classified by the investigator as not related to the study drug. There were no fatal AEs.

[5] Information from Summary of Clinical Safety, Clinical Overview, GAM10-08 Clinical Study Report, and Risk Management Plan, Version 11.2 for BLA 125062/674 and 674.5.

The expansion of the indication to include dermatomyositis is based on Study GAM10-08. The study included 95 patients who were randomized to receive Octagam 10% or placebo every 4 weeks for the 16-week First Period of the study. In the 24-week open-label Extension Period of the study, all the patients received Octagam 10%. The subjects were 75% female and ranged in age from 22-79 years old. They were 92% White, 5% Black/African-American, 2% Asian and 1% Other.

During the study, 84 (88.4%) of the patients had at least one treatment emergent adverse event (TEAE). Eighty-two (86.3%) of the patients had a suspected adverse drug reactions (ADR), which included 76 (80%) patients with infusional AEs, defined as onset during or within 72 hours after the infusion. The most common drug-related (as assessed by investigators) AEs were headache (42%), pyrexia (19%), and nausea (16%). There were 22 serious TEAEs reported in 14 (14.7%) patients during the Overall Period. There were 25 TEAEs that led to the discontinuation of the study drug in 13 (13.7%) of patients. There were no fatal TEAEs. There were no hemolytic transfusion reactions. There were 6 (6.3%) patients in the Octagam 10% group who had 8 thromboembolic events (TEEs) in the study. Two of the patients had both a pulmonary embolism and a deep vein thrombosis. The other four events, which occurred in 1 patient each, were cerebrovascular accident, cerebral infarction, pulmonary embolism, and hypoaesthesia. Six of the eight TEEs were considered by investigators related to the study drug. The two other TEEs were pulmonary embolus and deep vein thrombosis that occurred in a single patient 51 days after the last Octagam infusion. Of note, during the study, there was a protocol amendment based on an FDA recommendation that reduced the maximum allowed infusion rate from 0.12 mL/kg/min to 0.04 mL/kg/min. The exposure-adjusted incidence rates of TEEs in the study was lower after the change (1.54/100 patient months before the reduced rate versus 0.54/100 patient months after the reduced rate).

5 POSTMARKETING DATA

Octagam has been marketed in the US since 2004, first as Octagam 5% and then also as Octagam 10%. Many postmarketing reports do not clarify which concentration a patient received. FDA surveillance monitors both concentrations of Octagam together under the same license number. Searches in FAERS through Mercado and data mining through Empirica were performed on June 15, 2021. Data mining for Octagam, with a data lock point of June 13, 2021, identified 58 preferred terms with a disproportional reporting alert for Octagam (an EB05>2.0; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). [6] There were no new safety concerns from review of these PTs. The 15 Standard MedDRA Queries (SMQ)

[6] Data mining conducted using the Product Name (S) run in Oracle Empirica Signal. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point of June 13, 2021. Data mining is subject to a variety of limitations. Findings should be regarded as “hypothesis generating” and do not imply causality.

that were disproportionally reported based on those preferred terms were primarily related to hypersensitivity reactions, central nervous system disorders including embolic/thrombotic events, liver disorders (many related to passive transfer of antibodies affecting hepatitis serology results), and noninfectious [aseptic] meningitis. These issues are all common, labeled events for immune globulins, including Octagam.

There are 167 reports in FAERS for Octagam and the embolic and thrombotic events SMQ [narrow], with many reports additionally falling under associated SMQ's like central nervous system vascular disorders [narrow]. Following the increase in TEE reports with Octagam 5% in 2010 and the subsequent manufacturing modification made prior to the return to market in 2011, the sponsor conducted a safety postmarketing requirement (PMR) study under the Food and Drug Administration Amendments Act (FDAAA) called GAM5-28. This study was completed in 2020. The study did not show any increased risk of a TEE after Octagam 5% compared to other US-licensed IVIG products.

There are 336 FAERS reports for the SMQ of hypersensitivity [narrow] for Octagam, with 24 reports listed under anaphylactic/anaphylactoid shock conditions and 24 under anaphylactic reaction. Over the last 5 years, there have been three clusters of increased reports of hypersensitivity reactions after specific individual lots of Octagam. The sponsor and the FDA have assessed these lots associated with the clusters of hypersensitivity events and have not been able to determine the underlying root cause. Four lots have been voluntarily withdrawn from the market due to increased reporting associated with these three clusters. The sponsor (b) (4) (b) (4) There have not been any hypersensitivity clusters noted in the last 2 years for Octagam. This issue of increased hypersensitivity reactions after specific lots has been seen with other brands of immune globulin as well. Hypersensitivity reactions, including anaphylaxis, is a labeled event for Octagam. FDA continues to monitor lot related AEs under routine safety surveillance activities for Octagam.

There are 8 cases with the PT of haemolysis for Octagam in a FAERS search with a data lock point of June 13, 2021. There are 10 additional cases with the SMQ search for haemolytic disorders [narrow]. All 18 of these cases are foreign reports. They primarily describe hemolytic anemia occurring after Octagam. Hemolysis is a labeled event for all IVIG products.

For other identified and potential risks discussed below, FAERS searches identified the following number of reports. There are 19 reports in FAERS for Octagam and the noninfectious meningitis SMQ [narrow]. There were 21 reports for Octagam and the SMQ acute renal failure [narrow], with 6 of these reports appearing to be duplicates of the same event. There were no reports identified in FAERS for Octagam and the PT of transfusion-related acute lung injury.

6 PHARMACOVIGILANCE PLAN

The sponsor submitted the EU Risk Management Plan, Version 11.1 along with a US Specific Addendum with this efficacy supplement. Following an Information Request by the Division of Epidemiology (DE), the sponsor revised the RMP and submitted Version 11.2. This new RMP Version 11.2 included the data from the completed study GAM10-08 and had several updates regarding the issue of TEEs. Following a second DE Information Request, the sponsor submitted RMP Version 11.2a with the addition of an area of missing information and two questions to the TEE follow-up questionnaire. The sponsor did not update the US Specific Addendum to align with the RMP, Version 11.2 or 11.2a. The US Addendum still uses an older data lock point of Sep 30, 2020. This review memo uses the more updated data from the RMP, Version 11.2a. The important identified and potential risks as well as the areas of missing information are listed on Table 2 and discussed below. The sponsor is planning to continue to address these risks with labeling and routine pharmacovigilance. In addition, the risk of TEEs will be further characterized by a follow-up questionnaire. There are no ongoing or proposed studies included in the pharmacovigilance plan.

Table 2: Applicant's Pharmacovigilance Plan for Important Risks

Type of Risk	Safety Concern	Planned Pharmacovigilance Activity
Identified	• Thromboembolic events • Aseptic Meningitis • Hypersensitivity reactions, including anaphylactic reactions • Renal failure • Interference with certain blood glucose tests • Hemolysis	Routine pharmacovigilance with a follow-up questionnaire for the risk of thromboembolic events only.
Potential	• Suspected transmission of pathogen infection • Interaction with live attenuated virus vaccines and serological testing • Transfusion-related acute lung injury (TRALI) • Neutropenia/Leukopenia	Routine pharmacovigilance
Area of Missing Information	• Safety in pregnant and breastfeeding women	Routine pharmacovigilance

A. Important Identified Risks

i. Thromboembolic Events

Thromboembolic events have been associated with intravenous immune globulin treatment. The potential mechanisms include increased plasma viscosity, arterial vasospasm, activated coagulation factor XI, and increased platelet number and activation. The risk of thromboembolic events may be increased with the administration of high dose and fast infusion rates. There was a total of (b) (4) thromboembolic events classified as related to Octagam in (b) (4) of the (b) (4) patients in the (b) (4) completed clinical trials. That is a rate of 0.9% of patients treated and 0.14% of infusions. As discussed in the Regulatory History section above, the postmarketing period for Octagam 5% had an increased incidence of TEEs in 2010. Octagam 5% was voluntarily withdrawn from the market and manufacturing steps to reduce the level of factor XIa present were implemented. Since the return to market in 2011, Octapharma has received 93 reports in their pharmacovigilance database worldwide of suspected TEEs assessed as related to Octagam. These reports include both Octagam 5% and Octagam 10%, but Octagam 10% was not approved in the US until 2014. The sponsor also conducted a safety PMR study which did not identify an increased risk of TEEs after Octagam 5% compared to other US-licensed IVIG products.

This risk is especially important as patients with dermatomyositis are already predisposed to having TEEs. There is a general boxed warning for thrombosis in the Octagam label. In the RMP, Version 11.2, the sponsor added a statement that the Summary of Product Characteristics (SmPC) now highlights that patients with dermatomyositis are at increased risk for TEEs and recommends careful monitoring as well as not exceeding an infusion rate of 0.04 mL/kg/min. After an Information Request to the sponsor, the sponsor added additional rate of administration information to the US package insert, stating that the maintenance infusion rate for the dermatomyositis indication should not exceed 0.04 mL/kg/min.

In addition to labeling and routine pharmacovigilance, the sponsor is planning to use a follow-up questionnaire for reports of TEEs. This questionnaire asks about risk factors for TEEs, medication exposure, and specifics about the thromboembolic event. DE sent Information Requests to the sponsor and, in response, questions on the indication for treatment and the infusion rate were added to the questionnaire. Additionally, the sponsor will discuss interval and cumulative information related to the risk of TEE by treatment indication in the periodic safety reports.

ii. Aseptic Meningitis

While the biologic mechanism of aseptic meningitis after IVIG treatment is not fully understood, there are several proposed theories that include immune globulin aggregates that activate the complement system, local immune reaction to the IgG in the cerebrospinal fluid, and immune globulin interaction with the

meningeal vessel endothelium. Most cases of aseptic meningitis resolve without sequelae. There were (b) (4) reports of aseptic meningitis in the (b) (4) Octagam clinical trials. This results in a 95% CI of 0.004% - 0.13% per infusion. The sponsor has received 106 reports of suspected aseptic meningitis during post-marketing surveillance. That results in a frequency of 1 case per 45,366 infusions. Using a slow infusion rate, hydrating the patient, and premedicating the patient can reduce the risk of aseptic meningitis. Aseptic meningitis is included in the Warnings and Precautions section of the Octagam 10% label.

iii. Hypersensitivity reactions, including anaphylactic reactions

Introducing a protein into the body always raises the possibility of an allergic reaction. There were (b) (4) (5.6%) patients with a total of (b) (4) hypersensitivity reports among the (b) (4) patients in the clinical trials. The sponsor's post-marketing data has shown a frequency of 1 hypersensitivity reaction reported per 3,465 infusions. Patients with anti-IgA antibodies or IgA deficiency are at a higher risk of hypersensitivity reactions. Premedication with corticosteroids and antihistamines can reduce the risk. Hypersensitivity reactions are listed in the Warnings and Precautions section of the label.

iv. Renal Failure

Renal failure has been seen with other IVIG products, especially when the stabilizer sucrose is present. While Octagam does not contain sucrose, the maltose found in Octagam can also cause osmotic injury to the renal tubules. There were no reports of acute renal failure in the Octagam clinical trials. The sponsor has received 31 postmarket reports of suspected renal failure that were medically assessed by Octapharma as indicative of a safety concern. This results in a frequency of 1 per 155,122 infusions. There were 16 unique reports identified on a FAERS search for Octagam and the SMQ acute renal failure. The risk can be reduced with slow infusion rates, hydration, laboratory monitoring, and discontinuation if renal function decreases. Renal failure has a boxed warning in the Octagam 10% package insert. The package insert also includes instructions in the Administration section on the maximum infusion rate in patients at risk of renal dysfunction.

v. Interference with certain blood glucose tests

The maltose in Octagam 10% can cause some glucose monitoring systems to give results of falsely elevate blood glucose. This can lead to hypoglycemia not being recognized or high doses of insulin being given unnecessarily and causing hypoglycemia. When a diabetic patient is receiving Octagam 10%, blood glucose should be monitored using only a glucose-specific method. There were no reports of interference with blood glucose tests during the clinical trials. The sponsor has received 19 reports of possible interference with blood glucose tests in the postmarket setting, resulting in a reporting frequency of 1 in 253,093 infusions. There is a section on blood glucose monitoring in the Octagam 10% Warnings and Precautions.

vi. Hemolysis

The anti-A and anti-B isoagglutinins and resulting phagocytosis of antibody-coated red blood cells can cause hemolytic anemia from IVIG infusions. This hemolysis can be subclinical or it can result in severe hemolysis and anemia. There were no reports of hemolysis during the clinical trials. The sponsor has received 47 postmarket reports that it determined to be suspected hemolysis in the post market setting. This results in a reporting frequency of 1 in 102,314 infusions. As described in Section 5 above, there are 18 Octagam cases for the haemolytic disorders SMQ in FAERS. Hemolysis is listed under the Warnings and Precautions section of the package insert. The section includes risk factors (receipt of high dose, having a non-O blood group, having an underlying inflammatory state) for hemolysis and suggestions for laboratory monitoring in high risk patients.

B. Important Potential Risks

i. Suspected transmission of pathogen infection

Octagam utilizes multiple measures to prevent infectious agents including screening donors, testing donations and plasma pools, and three manufacturing steps for viral reduction (cold ethanol fractionation, S/D treatment, and pH 4 treatment). Steps to (b) (4) (b) (4) are also included in Octagam's manufacturing. Octagam has been used for approximately 4.7 million infusions over the last 25 years and there have been no cases of transfusion-associated vCJD transmission for Octagam reported to Octapharma. Transmission of pathogen remains a potential risk for the product derived from human plasma. There were no reports of suspected transmission of pathogens in the clinical trials. The sponsor has received 60 reports of possible suspected transmission of a pathogen, but none of these was determined to be certainly, probably, or possibly related to Octagam. The US package insert includes transmission of infectious agents in the Warnings and Precautions section of the label.

ii. Interaction with live attenuated virus vaccines and serological testing

As Octagam 10% is an immune globulin, administering Octagam 10% leads to passive transfer of antibodies. These transferred antibodies can cause serological test results to be positive even though the patient may not be infected with the infectious agent. Direct or indirect antiglobulin (Coombs') tests may appear positive from the passive antibody transfer. Transferred antibodies may also inhibit the response to live vaccines such as the measles, mumps, and rubella vaccine. There were no reports of interaction with live attenuated virus vaccines or serological testing in the Octagam clinical trials. The sponsor has received 28 reports in the post-market setting for this issue. The results in a reporting frequency of 1 in 171,472 infusions. The label states that live viral vaccines should be delayed at least 3 months following Octagam 10% treatment.

iii. Transfusion-related acute lung injury (TRALI)

A patient can experience noncardiogenic pulmonary edema, referred to as transfusion-related acute lung injury (TRALI) following any intravenous immune globulin. There were no reports of TRALI in the Octagam clinical trials. The sponsor has received 4 reports of suspected TRALI in the postmarket setting. This results in a reporting frequency of 1 in 1.2 million infusions. No reports for the PT transfusion-related acute lung injury were identified on a FAERS search, as described in Section 5 above. The Warnings and Precautions section of the PI includes information on monitoring for TRALI.

iv. Neutropenia/Leukopenia

There are several potential mechanisms for neutropenia/leukopenia with IVIG including granulocyte activation with increased margination, autoantibodies working with proinflammatory cytokines, and antineutrophil antibodies. There were 4 reports of neutropenia/leukopenia in the clinical trials. The sponsor has received 47 reports of neutropenia/leukopenia, resulting in a reporting frequency of 1 in 102,314 infusions. Risk factors include a history of cancer, autoimmune diseases, and bone marrow conditions. Pretreatment with corticosteroids can decrease the risk. Leukopenia is included in the Postmarketing Experience section of the package insert.

C. Areas of Missing Information

There were no areas of missing information listed in the Octagam Risk Management Plan, Version 11.2. Previous versions of the RMP listed areas of missing information including: safety in elderly patients, safety in pregnant or breastfeeding women, off label use, and safety in patients with renal and hepatic impairment. These different areas of missing information were removed from the RMP starting in 2018, with one issue, safety in patients with renal and hepatic impairment, being the last to be removed with RMP, Version 11.1. With the current submission, DE sent an Information Request to the sponsor communicating that safety in pregnant and breastfeeding women should be included as an area of missing information. The sponsor agreed, and this area of missing information was added back into the RMP with Version 11.2a. This area of missing information is included in Section 8 of the US Package Insert.

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor's Risk Management Plan, Version 11.2a, includes important updates with data on study GAM10-08, labeling regarding the maximum infusion rate for dermatomyositis patients, and the use of a follow-up questionnaire for TEE patients. The US Specific Addendum to the EU-RMP was not updated with Versions 11.2 or 11.2a. This RMP review memorandum is based on Version 11.2a, but the sponsor should update the US Specific Addendum to include the GAM10-08 study results and the additional TEE-related measures presented in the RMP, Version 11.2a.

The sponsor's Risk Management Plan includes the identified risks and potential risks that are common for all immune globulin products and several that are specific for Octagam. The identified and potential risks have been relatively well characterized for immune globulins across more than 10 US licensed products, some of which have been licensed for several decades.

Thromboembolic events have been the most significant safety concern for Octagam since licensure. The issue of increased TEEs seen with Octagam 5% in 2010 was addressed by a manufacturing change. Thromboembolic events continue to be a risk for all immune globulins, but postmarket surveillance and the Octagam 5% safety PMR study do not indicate Octagam has a higher risk than other immune globulin products. Certain factors are known to increase the risk of TEEs with the use of immune globulin. Many of those factors are specific to the patient's medical history including obesity, advanced age, hypertension, diabetes, and a history of thrombotic events. The Octagam package insert includes information on these patient-specific risks as well as recommendations for reducing the infusion speed and total dose in settings where thrombosis is considered to be a high risk. Patients with dermatomyositis are at an increased risk for TEEs due to their underlying disease so the warnings in the label regarding limiting the maximum infusion rate and dose should apply to all dermatomyositis patients. The RMP, Version 11.2a, specifically mentions a section added in the SmPC that states that patients with dermatomyositis are at increased risk for TEEs and should have a maximum infusion rate of 0.04 mL/kg/min. During labeling discussions for the current supplement, the sponsor added this more specific language regarding the maximum infusion rate for dermatomyositis patients to the revision of the US package insert, as well. The sponsor's follow-up questionnaire on reported TEEs will provide further characterization of these events. In response to DE's Information Request, the sponsor appropriately added questions on the indication and the infusion rate to the questionnaire. With the expansion of the indication to include dermatomyositis, it is important to understand if patients that are treated for that indication are having increased TEEs compared to patients being treated for primary immunodeficiency or other indications. The use of warnings in the label, a maximum infusion rate, and a follow-up questionnaire are appropriate mitigation methods considering the known individual increased risk of TEEs with dermatomyositis and with the use of IVIG. In addition, in the periodic safety reports, the sponsor agreed to provide an assessment and analysis of the risk of thromboembolic events after Octagam, specifically in patients with dermatomyositis, including a summary of interval and cumulative information related to this risk.

The other identified risks for Octagam that are commonly seen with other IVIG products, as well, are aseptic meningitis, hypersensitivity reactions, renal failure, and hemolysis. The issue of interference with certain blood glucose tests is specific to Octagam as it contains maltose.

The potential risks outlined in the Octagam RMP are: suspected transmission of pathogen infection, interaction with live attenuated virus vaccines and serological testing, transfusion-related acute lung injury (TRALI), and neutropenia/leukopenia. All of these potential risks have been reported after other immune globulins and are appropriate to include as potential risks with Octagam. There has not been evidence these have risen to the level of identified risks for Octagam.

In the postmarket setting, IVIG is frequently used for indications beyond what is approved in the US package insert. As a result, there have been postmarketing safety data that have included a wider range of patients than in the clinical trials. That has allowed the sponsor to gradually compile data on the original areas of missing information. Therefore, the sponsor no longer included any areas of missing information in the RMP, Version 11.2. Considering Octagam 5% has been approved in the US for 16 years and Octagam 10% since 2014, it is reasonable that some areas of missing information have been addressed. There is a specific concern for use of immune globulins in patients with renal disease. As renal dysfunction has a black box warning for immune globulins and the Octagam label specifically discusses monitoring renal function, the risk is known and risk mitigation has occurred through labeling. It is appropriate to remove patients with renal disease from the areas of missing information.

Regarding another special population that was previously listed as an area of missing information, the Octagam package insert lists use in pregnant and lactating populations as having no human data available to assess the presence or absence of a risk. Therefore, safety of Octagam in pregnant and breastfeeding women should remain an area of missing information in the RMP. The sponsor has added that area of missing information back in with RMP, Version 11.2a.

There have not been any other safety issues beyond those discussed in this memorandum that have emerged as concerns for Octagam through postmarketing surveillance. As the RMP, Version 11.2a, is adequate for this efficacy supplement, DE will follow-up with the sponsor at a later date to obtain an updated US Specific Addendum with a data lock date that aligns with the RMP.

8 OBE/DE RECOMMENDATIONS

- DE agrees with the routine pharmacovigilance activities proposed by the applicant in the Risk Management Plan, Version 11.2a, along with adverse event reporting as required under 21CFR600.80. In the periodic safety reports, the sponsor will also provide an assessment and analysis of the risk of thromboembolic events after Octagam, specifically in patients with dermatomyositis, including a summary of interval and cumulative information related to this risk.

- The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety postmarketing requirement (PMR) or postmarketing commitment (PMC) study at this time.