



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

MEMORANDUM

Date: January 7, 2013

From: Michael D. Nguyen, MD
Deputy Director, Division of Epidemiology

To: 125416/0

Through: David Martin, MD, MPH
Director, Division of Epidemiology

Subject: Pharmacovigilance Plan Review Octaplas™

Applicant: Octapharma

Product: Octaplas™ solvent/detergent (S/D) treated human plasma

Action Due Date: Original: October 22, 2012
Extended: January 21, 2013

1. INTRODUCTION

Octaplas™ is a solvent/detergent (S/D) treated, blood group specific, pooled human plasma product developed by Octapharma. Octaplas™ (henceforth Octaplas) is available in 200mL doses for intravenous administration, stored in frozen polyvinyl chloride blood bags. The product consists of all normal components of plasma, including albumin, immunoglobulins and other globulins, coagulation factors, complement factors and their inhibitors. Octaplas is produced from plasma pools consisting of 630 to 1520 single donor units of the same blood type and was designed as an alternative to single-donor fresh frozen plasma (FFP). Octaplas contains the following excipients: sodium citrate dehydrate, sodium dihydrogen phosphate dehydrate, and glycine. Although donor selection and screening have considerably improved the safety of FFP over time, Octaplas has several biochemical advantages of over FFP:

- a. **Enveloped viral inactivation.** Solvent/detergent treatment inactivates enveloped pathogens such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV) and West Nile Virus through nonselective disruption of viral lipid membranes
- b. **Non-enveloped virus control.** Reduced transfusion associated non-enveloped viral transmission including Hepatitis A Virus (HAV) and Parvovirus B19 through routine nucleic acid amplification (NAT) screening and a minimum specification for neutralizing antibodies levels in the final product against HAV and Parvovirus B19
- c. **Reduced Transfusion Related Acute Lung Injury (TRALI) risk.** Plasma pooling during production dilutes anti human neutrophil antigen antibodies (HNA) and anti-human lymphocyte antigen (HLA) antibodies hypothesized to mediate TRALI risk
- d. **Reduced allergic reactions.** Whole cells and cell fragments are removed by size-exclusion filtration during manufacturing which may theoretically reduce allergic reactions.

Although S/D treatment is useful for viral inactivation and removal, it impacts product quality and safety by reducing levels of Protein S (PS) and plasmin inhibitor (PI). This is notable because low Protein S levels were causally related to thromboembolic events in a predecessor S/D plasma product (PLAS+SD) manufactured by V.I. Technologies.^{1,2} PLAS+SD was FDA licensed in 1998, distributed by the American Red Cross, and voluntarily withdrawn in the United States (US) in 2004. Similarly, other plasma pathogen inactivation treatments, such as methylene blue photo-treatment, decrease coagulation Factor VIII and fibrinogen levels. If approved, Octaplas would be the only S/D treated plasma approved by FDA. For Octaplas, the biochemical activities for key plasma proteins are comparable to FFP (see Table 1), except for:

- a. PS levels in Octaplas are within the lower limit of the reference range (30–35% lower than FFP)
- b. PI levels are below the lower limits of the reference and FFP ranges (less than ~50% of normal)

¹ MedWatch Alert. A cluster of 6 serious adverse events at a single institution during orthotopic liver transplantation. All six patients died due to thrombotic events or excessive bleeding during the transplant procedure. All patients received intra-operative PLAS+SD along with multiple other blood components. October 20, 2000.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173238.htm>

² MedWatch Alert. Addition of a Boxed Warning and a Strengthened Warning Section in the Labeling for PLAS+SD (Pooled Plasma, (Human) Solvent Detergent Treated). March 29, 2002.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm155086.htm>

Table 1: Protein S (PS) and Plasmin Inhibitor (PI) Levels in Octaplas

Parameter	Reference (N=100)	Octaplas (n=12)	FFP (n=12)
Plasmin Inhibitor (IU/mL)	0.72 – 1.32	0.48 (0.30 – 0.50)	1.04 (0.95 – 1.18)
Protein S (IU/mL)	0.56 – 1.68	0.61 (0.50 – 0.70)	1.03 (0.71 – 1.39)

Data from Jain, Nisha. "Overall FDA Conclusions: Assessment of the Relative Benefits and Risks." Blood Products Advisory Committee Meeting, September 20, 2012.

1.1. Regulatory History

This biologic licensure application (BLA) is complicated by a product development program that began in the 1990s and consists of multiple product generations (see Table 2). Only one of the studies was conducted under an investigational new drug application (IND) (LAS 203 was conducted under IND 13956), with the associated guidance and support of the FDA. The sponsor is seeking approval only for Octaplas™ (which was named OctaplasLG throughout the BLA documents) not the original Octaplas®. FDA has determined that the biochemical properties common to product generations 1, 2a and 2b are sufficiently similar to enable all studies using prior product generations to support the evaluation of safety and efficacy of Octaplas.³

- Octaplas
 - first licensed in Germany 03 Nov 1989; currently approved in 19 countries⁴
 - blood group specific, S/D treated (-(b)(4)-) virus-inactivated pooled plasma (without any specific prion removal column)
- OctaplasLG (now renamed Octaplas™)
 - first licensed 01 June 2009; subsequently approved in 11 countries
 - blood group specific, S/D treated (1–1.5 hours) virus-inactivated pooled plasma with a manufacturing process that includes chromatographic step for the selective binding of prions to a ligand in an attempt to reduce the risk of variant Creutzfeldt-Jakob disease
 - reduced S/D treatment time designed to improve the concentration of S/D labile plasma proteins, such as plasmin inhibitor (PI or alpha-2 anti-plasmin) and Protein S.
- uniplas®/uniplasLG®
 - Not blood group specific - differs from Octaplas®/Octaplas only in that anti-A and anti-B antibodies are removed to make them universally transfusable.
 - uniplas®/uniplasLG® are not licensed in the US or European Union

³ FDA Blood Products Advisory Committee Briefing Package: September 20, 2012.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm298652.htm>

⁴ Octapharma Blood Products Advisory Committee Briefing Package: September 20, 2012.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm298652.htm>

Table 1: Generations of Solvent Detergent Plasma (SDP*) Products Produced by Octapharma

Generation**	Product Name	S/D Treated	Product Formulation	Blood Group Specific	LG Chromatography	Current Availability Status
1	Octaplas®	Yes	lyophilized	Yes	No	No
2a	Octaplas®	Yes	liquid, frozen	Yes	No	Yes, since 1992 in EU
2b	OctaplasLG	Yes	liquid, frozen	Yes	Yes	Yes since 2009 in EU
3a	uniplas	Yes	liquid, frozen	No	No	No
3b	uniplasLG	Yes	liquid, frozen	No	Yes	No

* SDP will be used to refer to all Generations of the Octapharma solvent/detergent treated plasma product.

** For all generations, the time until a plasma donation is frozen (core temperature -25°C) is 8 to 24 hours for recovered plasma and 18 hours (freezing process has to start after 6h at the latest) for source plasma. Octapharma does not differentiate between 8 hours and 24 hours plasma in their warehouse.

EU = European Union

1.2 Proposed and Actual Product Indications

Octapharma originally proposed to seek only two of FFP's six indications for Octaplas (see Table 3). However, during the course of the BLA, the indications were narrowed to explicitly cover only the populations studied in the clinical development program:

1. Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease and in patients undergoing cardiac surgery or liver transplantation;
2. Transfusion or plasma exchange in patients with Thrombotic Thrombocytopenic Purpura (TTP).

Table 3: Proposed Indications for Octaplas

	Indication	FFP	Octaplas
1	Management of preoperative or bleeding patients who require replacement of multiple coagulation factors	X	X
2	Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura)	X	X
3	Patients undergoing massive transfusion who have clinically significant coagulation deficiencies	X	
4	Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect	X	
5	Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available	X	
6	Management of patients with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable	X	

1.3 Advisory Committee Meetings

On 20 September 2012, FDA sought the advice of the Blood Products Advisory Committee (BPAC) on whether the BLA data support that Octaplas “has an acceptable safety profile and is effective in the patient populations for which indications are being sought.”³ The decision to take the application to BPAC was due to the limited amount of safety and efficacy information from controlled studies and the use of multiple product generations in the development program. Moreover, Octaplas is a unique product in that it is plasma-derived and manufactured to minimum release specifications, analogous to a licensed biologic therapeutic, but will be clinically used as a substitute for fresh frozen plasma, a blood component that FDA approved under a different regulatory pathway. (Please see the BPAC transcript for full details and discussion.) The 15 member advisory committee containing representatives from academia, Centers for Disease Control and Prevention, National Institutes of Health, state health departments, the Armed Services Blood Program Office, consumer, and industry, voted on 3 questions and provided advice on 1 question:

Table 4: Voting Results at the Blood Products Advisory Committee, 20 September 2012

Committee Question	Yes	No	Abstain
1) Do the data show that OctaplasLG is effective			
a) for the management of preoperative or bleeding patients who require replacement of multiple coagulation factors?	8	4	3
b) as substitution of intentionally removed plasma (e.g. plasma exchange in patients with TTP)?	10	3	2
2) Do the data show that OctaplasLG has an acceptable safety profile for the indications stated in question 1?	12	3	0
3) If the answer to question 1 or question 2 is no, what additional studies should be performed premarketing for the proposed indications?	Not applicable		
4) Please comment whether safety monitoring would be needed post approval specifically to monitor:	15*	0	0
a) thromboembolic events?			
b) excessive bleeding?			
c) transmission of HEV?			

** Only one vote was taken for the entire question number 4.*

1.4 Objectives

This memorandum follows a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review Octapharma’s pharmacovigilance plan. There are two objectives:

- a. Review and identify the limitations to the overall clinical safety database
- b. Assess the adequacy of Octapharma’s proposed pharmacovigilance plan, given the limitations of the product development program and the advice from the BPAC committee

2. MATERIALS AND METHODS

2.1 Evaluation Criteria and Regulatory Authority

The regulatory recommendations in this memorandum are based on criteria described in Postmarketing studies and clinical trials — Implementation of Section 505(o) the Federal Food, Drug and Cosmetic Act (July 2009). This guidance describes FDA’s authority to require postmarketing studies or clinical trials at

the time of approval or after approval if FDA becomes aware of new safety information. Such studies or clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicate the potential for a serious risk

2.2 Materials Reviewed

Source	Document Reviewed
Octapharma	Proposed Pharmacovigilance Plan, Report Date 03 July 2012
Octapharma	Overview of Safety for Octaplas (27 Oct 1989 to 31 Oct 2010)
Octapharma	Periodic Safety Update Report (01 Jan 2011 to 30 Jun 2011)
Octapharma	Periodic Adverse Experience Report (16 Feb 2012 to 15 Jun 2012)
Octapharma	BLA Section 2.7 Clinical Summary
Octapharma	Octapharma Issue Summary, BPAC 20 Sept 2012
Octapharma	Response to FDA Information Request, 8 Aug 2012
Octapharma	Response to FDA Information Request, 27 Aug 2012
FDA	FDA Issue Summary, BPAC 20 Sept 2012
Publication	De Jonge J, et al. Fibrinolysis during liver transplantation is enhanced by using solvent/detergent virus-inactivated plasma (ESDEP®). <i>Anesth Analg</i> . 2002; 94:1127-31.
Publication	Yarranton H, et al. Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura. <i>Br J Haematol</i> . 2003 Jun;121(5):778-85.
Publication	Magner JJ, et al. Fatal fibrinolysis during orthotopic liver transplation in patients receiving solvent/detergent-treated plasma (Octaplas). <i>J Cardiothorac Vasc Anesth</i> . 2007 Jun;21(3):410-3
Publication	Yves O, et al. Changing trends in transfusion practice in liver transplantation. <i>Curr Opin Organ Transplant</i> . 2008 Jun;13(3):304-9.
Publication	Hellstern P, et al. The Use of Solvent/Detergent Treatment in Pathogen Reduction of Plasma. <i>Transfus Med Hemother</i> . 2011;38(1):65-70.
Publication	Sabate A, et al. Coagulopathy management in liver transplantation. <i>Transplant Proc</i> . 2012 Jul-Aug;44(6):1523-5.
Publication	Seghatchian J, de Sousa G. Update on pathogen reduction technology for therapeutic plasma: an overview. <i>Transfus Apher Sci</i> . 2006 Aug;35(1):83-90.
Publication	Goodnough LT, Hill CC. Use of point-of-care testing for plasma therapy. <i>Transfusion</i> . 2012 May;52 Suppl 1:56S-64S.
Publication	Molenaar IQ, et al. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. <i>Am J Transplant</i> . 2007 Jan;7(1):185-94.
Publication	Bartelmaos T et al. Plasma transfusion in liver transplantation: a randomized, double-blind, multicenter clinical comparison of three virally secured plasmas. <i>Transfusion</i> . 2012 Sep 24.
Letter to the Editor	Solheim BG et al. Fibrinolysis During Liver Transplant and Use of Solvent/Detergent Virus-Inactivated Plasma (ESDEP®/Octaplas®) <i>Anesth Analg</i> . 2003 Apr;96(4):1230-1; author reply 1231-2.
Letter to the Editor	de Jonge et al. Liver transplantation, solvent-detergent treated plasma and antifibrinolytics. <i>Anesth Analg</i> . 2003 Apr;96(4):1231; author reply 1231-2.

3. PHARMACOVIGILANCE PLAN REVIEW

3.1 Clinical Safety Database

Octapharma submitted 17 total studies in support of licensure. Of these, OBRR determined that 9 studies were evaluable, totaling 528 subjects (see FDA Clinical Review for further details regarding exclusion).

Figure 1: Overview of Clinical Studies in Support of Licensure

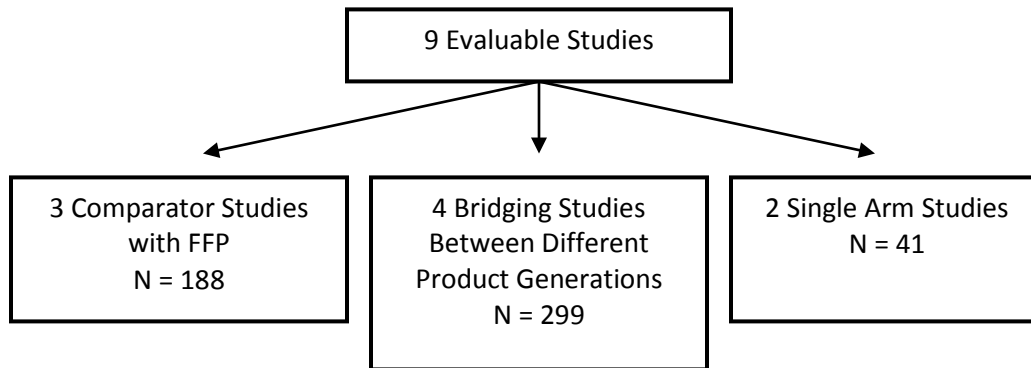


TABLE 5: Evaluable Studies in BLA

Study	Design	Products	Clinical Setting
Comparator Studies			
LAS-1-02-D 1998	Prospective, open-label, single-center	Total N: 67 Octaplas (G-2a): 36 FFP: 31	ICU post-open heart surgery
19/PLAS/IV/91 1992	Prospective, open-label, single-center	Total N: 66 Octaplas (G-1): 20 FFP: 20 No plasma: 26	Open heart surgery
LAS-1-03-UK 1995	Prospective, open-label, randomized, multi-center	Total N: 52 LD: 24 (Octaplas G2a: 13/FFP 11) LT: 25 (Octaplas G2a: 12/FFP 13) TTP: 3 (Octaplas G2a: 3)	Liver disease Liver transplantation TTP requiring plasma exchange or infusion
Bridging Studies			
UNI-101 1999	Prospective, randomized, controlled, blinded	Total N: 84 Octaplas (G-2a): 19 Uniplas: 36 no plasma: 29	Elective open heart surgery
LAS-201 2008	Observational, open-label, multi-center, sequential cohort	Total N: 125 Octaplas (G-2a): 65 OctaplasLG: 60	Any clinical condition with a need for plasma
LAS-203 2009	Prospective, randomized, open-label, controlled, cross-over, single center	Total N: 60 Octaplas (G-2a) OctaplasLG	Healthy volunteers
UNI-110 2009	Prospective, randomized, double-blind, controlled, cross-over, single center	Total N: 30 OctaplasLG uniplasLG	Healthy volunteers
Single Arm Studies			

Study	Design	Products	Clinical Setting
3PLASIV90 1990	Prospective, open-label	Octaplas (G-1) : 11	Hereditary or acquired coagulation factor deficiency
LAS-Study 1-D 1992	Prospective, open-label	Octaplas (G-1): 30	ICU patients with DIC

DIC: disseminated intravascular coagulation

3.2 Limitations to the Clinical Safety Database

The clinical database submitted for licensure has numerous limitations, including the lack of any pivotal Phase III trial, small sample sizes making them underpowered for efficacy, lack of predefined clinical efficacy endpoints (all but one study used laboratory endpoints), lack of predefined hypotheses, studies which were conducted on different patient populations than those within the intended indications), and use of multiple different products.

- a. **Comparator studies.** All 3 of the actively controlled studies were unblinded, which can introduce bias into the safety assessment since investigators are aware of patient therapy prior to assigning and adjudicating relatedness to product exposure for all adverse events. Only 1 of the studies was randomized, and the non-randomized studies failed to prespecify a design to reduce systematic bias and confounding. None of the studies were hypothesis driven, which limits the determination of whether any differences in rates were observed by chance alone.
- b. **Bridging studies.** All 4 studies compared different generations of biochemically similar solvent detergent products manufactured by Octapharma, rather than placebo or a true active control such as FFP. Since none of these products are US-licensed, the safety data collected is evaluated against an unknown internal comparator. Moreover, two of the four studies were on healthy subjects, and therefore the data do not contribute to the evaluation of safety in the intended patient population given all complex coagulopathies, hemostatic disorders, and associated comorbidities, and concomitant medications in patients requiring FFP.
- c. **Single arm studies.** Both studies were conducted 20 years ago (1990 and 1992) and evaluated a product (G-1a) which is no longer marketed. Although the data from prior product generations are considered equivalent, changes may have occurred in clinical practice patterns and use of concomitant medications in these open labeled studies.

The pooled safety database is presented in Table 4. Although there appear to be imbalances in the rates of allergic-type reactions (urticaria, pruritus) and headache, these were driven principally by studies in healthy volunteers (LAS 203 and UNI-101), where patients were not pre-medicated before plasma infusion as they would likely be in clinical practice. This was done to ensure that no adverse events were being masked, and therefore these rates are not necessarily representative of the true adverse event rates for Octaplas during usual clinical practice.

Notably, no cases of hyperfibrinolysis or TRALI were noted in either study or control groups, consistent with either the low incidence rate or small sample sizes in the clinical studies.

A total of 19 deaths were reported in the clinical trials: 7 after Octaplas®, 1 after uniplas® and 11 after FFP. All cases were assessed as unrelated to study treatment. Please see the FDA clinical review for further details.

Table 6: Pooled Safety Database

Adverse Event	Octaplas (N=120) No. (%)	Octaplas® (G1,2a) (N=239) No. (%)	FFP (N=75) No. (%)	No Plasma (N=55) No. (%)
Anaphylactoid reaction	0	1 (0.4%)	0	0
Pruritis	2 (1%)	3 (1%)	0	0
Urticaria	19 (15%)	13 (5%)	0	0
Fever	0	1 (0.4%)	0	0
Revision for Bleeding	0	6 (2%)	4 (5%)	2 (3%)
Nausea	4 (3%)	2 (0.8%)	0	0
Hemorrhage	0	1 (0.4%)	1 (1%)	0
Headache	19 (15%)	11 (4%)	0	0
Paraesthesia	21 (17%)	8 (3%)	0	0
TRALI	0	0	0	0
Hyperfibrinolysis	0	0	0	0

3.2 Octapharma Proposed Risk Management Plan

Table 7: Proposed Risk Management Plan

	Health Outcome	Action Plan
Important identified risks	1) Hypersensitivity and anaphylaxis 2) Venous thromboembolism	Passive surveillance
Important potential risks	3) General virus safety 4) Hemolytic transfusion reaction 5) TRALI 6) Excessive bleeding due to hyperfibrinolysis 7) ABO-incompatible Octaplas transfusion	Passive surveillance
Important missing information	8) Safety in pediatric, elderly and pregnant and nursing women	Passive surveillance

4. REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

4.1 Blood Products Advisory Committee Briefing Package

Two principal safety concerns arose during the evaluation of this application and summarized briefly below. Please see the BPAC issue summary pages 20 – 21 for further details.

1. Low Protein S levels and risk of thromboembolism. In 2003, Yarranton et al. published a retrospective review of venous thromboembolism after 68 consecutive patients with TTP who underwent plasma exchange therapy. A total of 8 chart confirmed VTE cases were noted: 5 deep vein thromboses (DVT), 1 pulmonary embolism (PE), 1 combined PE and DVT. The cases of VTE occurred an average of 53 days (range 14 to 161 days) after the first therapeutic plasma

exchange for the acute episode of TTP. Of 8 patients, 7 had Octaplas® G-2a and 1 had FFP as the last plasma infused prior to disease onset. Octaplas was the only plasma used for 3 of the patients with VTE. Notably, all 8 patients had significant precipitating factors that may have contributed to the adverse events:

- a. All patients with DVT had a history of central venous catheterization
- b. The one case of pulmonary artery thrombosis had a Swan-Ganz catheter
- c. 1 VTE occurred in a pregnant female
- d. All 8 patients had a history of immobility
- e. 3 patients had BMI > 30
- f. 1 patient was heterozygous for Factor V Leiden mutation

Yaranton et al. cited a prospective study of TTP patients in North America published in 2000 that reported a background rate of 3% of VTE for this population.⁵ By comparison, their retrospective review identified a rate of 12%.

The risk of thromboembolism is still a concern in this population, although it may be mitigated in Octaplas due to higher levels of PS.

2. Low PI (alpha-2 antiplasmin) levels and risk of bleeding (hyperfibrinolysis). Secondary hyperfibrinolytic states are associated with both chronic liver disease, as well as the anhepatic period during orthotopic liver transplantation due to decreased clearance of t-PA from the circulation as well as decreased hepatic synthesis of alpha-2-antiplasmin. There have been 2 literature reports of hyperfibrinolysis after Octaplas® use.

In 2002, De Jonge et al. reported a significantly elevated incidence of hyperfibrinolysis among Octaplas® recipients (15/20; 79%), compared to patients receiving FFP (6/21; 29%), who were undergoing orthotopic liver transplantation. Notably, in a subsequent letter to the editor, they offered key observations to explain their findings that were not stated in their original article:

- *During the study period, we experienced serious hemostatic problems with substantial blood loss. This may partly be attributed to the limited number of transplantations performed per year in our center at that time, the seriousness of pre-operative coagulation disorders in our patient population and the use of a standard liver transplantation technique without piggyback anastomosis. In patients with normal pre-operative coagulation tests and little blood loss, no fibrinolysis was seen using ESDEP plasma. The appearance of hyperfibrinolysis seemed related to the amount of blood loss.*
- *Since the introduction of a piggyback anastomosis technique without the need for retroperitoneal dissection, blood loss decreased importantly in our transplant center. As hemorrhage is no longer a main issue, attention must be paid to avoid thrombotic complications. The beneficial effect of routine use of a low dose Aprotinin regime using normal fresh frozen plasma was confirmed by Porte et al. in a multicenter study (3). In this study no differences in thrombotic complications between the placebo group and the Aprotinin groups were seen. We now have used the low dose Aprotinin scheme with ESDEP on a routine base in 120 patients, without thrombotic complications so far.*

⁵ Rizvi MA, Vesely SK, George JN, Chandler L, Duvall D, Smith JW, Gilcher RO. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. *Transfusion*. 2000 Aug;40(8):896-901.

Octapharma has included an appropriate warning about hyperfibrinolysis in the package label and has endorsed the routine administration of anti-fibrinolytic therapy routinely in this clinical setting.

Additionally, Magner et al. reported 2 cases of fatal fibrinolysis during liver transplantation in patients receiving Octaplas® in Ireland shortly after the nationwide adoption of Octaplas® as a substitute for FFP.

In contrast, Solheim et al. reported in a Letter to the Editor that the Norwegian experience with Octaplas® did not reveal any fibrinolysis concerns during the period of 1993 – 2001, during which 208 liver transplants were performed using Octaplas®.

- *We have with interest read the retrospective observational study by de Jonge et al. (1) of enhanced fibrinolysis during liver transplantation after use of solvent/detergent virus inactivated (SD) plasma. As the authors state, the production method for ESDEP®/Octaplas® (Octapharma, Vienna, Austria) reduces the content of α_2 -antiplasmin by up to 76% (2–6). α_2 -antiplasmin is a liver synthesized acute-phase serine protease inhibitor of plasmin (7).*
- *Following a decision by our Surgeon General in 1992, SD plasma has totally replaced FFP in Norway since 1993. Since then, more than 250,000 units of Octaplas® have been transfused. So far the product has been used in all types of patients, including neonates. No particular problems with fibrinolysis have been reported after Octaplas® transfusion, however, the serine protease inhibitor Aprotinin, is generally used in patients with severe liver failure (including liver transplantation) and in complicated repeat cardiac surgery. Allogeneic transplant surgery in Norway is centralized to our hospital. We have performed 208 liver transplants between 1993-2001 using Octaplas® without particular problems with fibrinolysis.*
- *Thus the Norwegian experience with Octaplas does not support the suggestion by de Jonge et al. for routine administration of antifibrinolytic drugs when using SD plasma produced by Octapharma.*

Table 8: Laboratory Diagnosis of Abnormal Fibrinolysis

Test	Primary hyperfibrinolysis	DIC	TTP
Platelet count	Normal	Decreased	Decreased
Fibrinogen	Decreased	Decreased	Normal
FDP	Increased	Increased	Normal
D-dimer	Increased	Increased	Normal
Antithrombin	Normal	Decreased	Normal
Schistocytes	Absent	Present	Present
Plasma clotting times	Prolonged	Prolonged	Normal
Euglobulin lysis time	Shortened	Shortened	Normal
ADAMTS13 level	Normal	Normal*	Low (usually <10 percent)*

DIC: disseminated intravascular coagulation; TTP: thrombotic thrombocytopenic purpura; FDP: fibrinogen degradation products; ADAMTS13: von Willebrand factor-cleaving protease (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

* May be reduced when bacterial sepsis is present.

• A normal plasma ADAMTS13 level does not exclude the diagnosis of TTP.

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4.2 CRMTS #6901 Meeting Response Memorandum

On 16 Dec 2008, FDA provided a written response to an Octaplas information package describing the path to licensure based on submission of a combination of data:

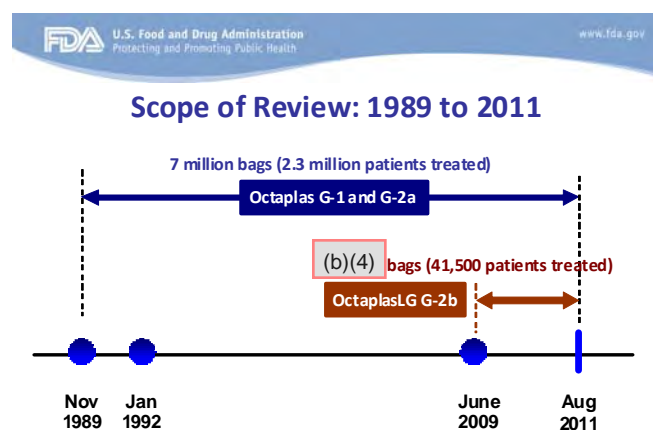
- 1) Final study reports for non-IND studies of Octaplas
- 2) Final reports for bridging studies to permit the conclusion that OctaplasLG is comparable to prior generations of Octaplas
- 3) Submission of European postmarketing surveillance safety data
- 4) Agreement to a postmarketing requirement (PMR) to conduct a phase IV clinical trial of the use of Octaplas in subjects undergoing orthotopic liver transplantation

5. POSTLICENSURE SAFETY REVIEW

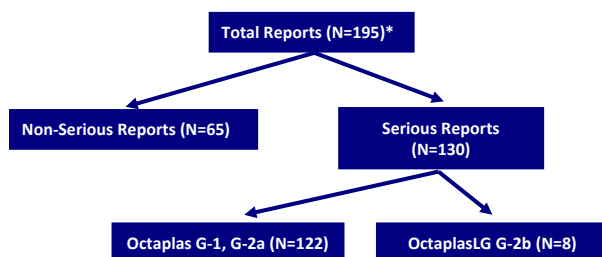
Octaplas®G-1 and G-2a and Octaplas post-licensure safety surveillance data:

- Over 21 years of postmarketing surveillance data are available for Octaplas G-1 and G-2a. Since the initial Octaplas approval on 27 October 1989, Octaplas®G-1 and G-2a have been approved in 28 countries worldwide, totaling 7 million units (200mL bags) sold and an estimated 2.3 million patients exposed.
- Over 2 years of postmarketing surveillance data are available for Octaplas (G-2b). Since the first approval in June 2009, Octaplas has been approved in 2 countries, totaling ----(b)(4)---- units (200mL bags) sold and an estimated 41,500 patients exposed.
- From 27 October 1989 to 31 August 2011, a total of 195 adverse event reports were received worldwide describing 407 types of events. Of these, 144 (74%) were spontaneous reports from healthcare providers, 36 (18%) from regulatory authorities, 13 (6%) from the medical literature, and 2 (1%) from clinical studies.

Figure 2: Slides 5 and 10 from OBE BPAC Presentation



Postlicensure Reports by Product — 1989 to 2011



* 195 reports consisted of a total of 407 preferred terms (most reports consisted of more than 1 symptom)

10

Table 8: Worldwide Summary of Serious Adverse Events for Octaplas® G-1, G-2a, G-2b — October 1989 to August 2011 (N=130)†

	Report Category	No. Unrelated Cases*		No. Related Cases**	
		G-1 and G-2a	G-2b	G-1 and G-2a	G-2b
1	Hypersensitivity reactions including anaphylactic and allergic reactions	2	0	42	5
2	Respiratory disorder (not elsewhere classified)	2	0	10	2
3	Circulatory overload	1	0	5	0
4	Seroconversions (passive transfer of antibodies)	0	0	5	0
5	Thromboembolism	0	0	4	0
6	Other (alkalosis, medication error, etc.)	2	0	2	1
7	Cardiac disorder (not elsewhere classified)	4	0	2	0
8	Isolated fever and chills	0	0	2	0
9	Citrate toxicity	0	0	1	0
10	Hyperfibrinolysis	0	0	1	0
11	TRALI	0	0	0	0
12	Hemolytic transfusion reaction	0	0	0	0
13	Suspected transmission of infectious agents	38	0	0	0
	TOTAL	49	0	74	8

* Classified as not related, unlikely, unclassifiable

** Classified as possible or probable

† All adverse event reports were represented only once except one case was listed twice as both a suspected transmission and hypersensitivity reaction.

The three most frequent serious adverse events reported after Octaplas G-1 and G-2a were hypersensitivity reactions, respiratory disorders, and circulatory overload. Reports of thromboembolism and hyperfibrinolysis, historically a source of concern with solvent/detergent-treated plasma products, were also detected.

Reviews of health outcomes of interest:

1. TRALI

- a. No cases reported that were causally related to Octaplas
- b. Many cases were “rule out TRALI” after patients experienced acute pulmonary edema
- c. High dosages and infusion rates can induce hypervolemia and pulmonary edema

2. Viral transmission

- a. No transmission of HIV, HBV, HCV or HAV has been observed

3. Acute hypersensitivity reactions

- a. Range from mild to serious
- b. Characterized by urticaria, fever, vomiting, hypotension, bronchospasm and dyspnea

4. Thromboembolism

- a. Majority of cases derived from a single case series of TTP patients receiving plasma exchange
- b. Many had underlying risk factors (e.g. oral contraceptive use, pregnancy, obesity, family history)

5. Hyperfibrinolysis

- a. Only 1 case reported in patient undergoing liver transplantation due to sporadic hepatitis C infection who received Octaplas (G2a)
- b. No cases have been reported after Octaplas (G-2b)

Notably, 2 out of 8 reports for Octaplas contained unlisted adverse events, as follows:

- **Convulsion:** A 44-year-old male patient, suffering from a bone marrow transplantation-associated thrombotic thrombocytopenic purpura (TTP), received plasmapheresis treatment with Octaplas (S/D treated plasma, 300 mL). During the infusion, the patient experienced severe generalized seizures. Plasmapheresis treatment was interrupted and a neurological examination was performed including a CT scan which did not disclose any findings. The patient completely recovered within 15 min and plasmapheresis treatment was continued a couple of hours later on the same day. The treating physician suspected the seizures to be related to the patient’s underlying TTP. Octapharma classified this case as serious, unlisted and possibly related to the administration of OctaplasLG due to the temporal relationship.
- **Dyspnea, Hypervolemia, [possible] Transfusion-related acute lung injury, Pneumonia, Lung infiltration, Malaise:** A 21-year-old female patient with acute myeloid leukemia was treated with platelet concentrates (2 units) and Octaplas (2 units). Subsequently, the patient developed dyspnea, malaise and pulmonary infiltrates. The treating physician suspected pneumonia with the differential diagnosis of TRALI. The hospital tested the platelet concentrate, Octaplas and the patient for HNA and HLA antibodies. Octapharma classifies this serious (reported as medically significant) case as unlisted and the symptoms possibly related to the administration of Octaplas due to the temporal relationship. The diagnosis of TRALI is considered highly unlikely due to negative HNA and HLA re-tests of the batch. Retests were performed internally, as well as in 2 external laboratories, and all found negative results for the respective antibodies.

Table 9: All MedDRA Preferred Terms Associated with the 62 Serious Unlisted Reports for Octaplas (G-1, G-2a) and OctaplasLG (G-2b) from Oct 1989 – Aug 2011

Category in Table 6 of Clinical Overview	Number of Unrelated Cases	Number of Related Cases
Suspected transmission of infectious agent	38	0
Hypersensitivity reactions including anaphylactic and allergica type of reactions	0	4
Seroconversions (passive transfer of antibodies)	0	5
Cardiac disorder (not elsewhere classified)	4	1
Respiratory disorder (not elsewhere classified)	1	1
Thromboembolism	0	4
Hyperfibrinolysis	0	1
TRALI	1	0
Other (alkalosis, medication error, etc.)	2	1

^ one case was listed twice as both a suspected transmission and hypersensitivity reaction

Deaths

Reports of deaths occurring in association with the administration of the Octaplas products have been few and most have been judged by the sponsor to be unrelated to the product. Table 10 summarizes those death reports where the fatality was judged by the sponsor to be possibly related to the infusion of the Octaplas product.

Table 10: Summary of Deaths Judged by Octapharma to be Possibly Related to Octaplas® G-1, G-2a or G-2b

Manufacturer Report Number	Adverse Event (MedDRA preferred term)
LAS-011-02-IRL	fibrinolysis, hemorrhage, coagulopathy
LAS-015-02-IRL	therapeutic response decreased, cardiac arrest, fibrinolysis
LAS-006-07-DE	acute pulmonary edema
LAS-002-06-IRL	hypotension, cardiac arrest
LAS-024-10-LU	pulmonary edema, transfusion related circulatory overload

In summary, compared to the known safety profile from the clinical development program, no new safety signals were identified after >2.3 million patients have been exposed to all Octaplas formulations. However, passive surveillance data serves as a safety net after licensure for rare or unusual events and should be interpreted as hypothesis generating. Although passive surveillance cannot determine the true rates of adverse events, the international postlicensure data provided by Octapharma are reassuring.

6. INTEGRATED RISK ASSESSMENT

The primary strength of this product application is the extensive postmarket experience internationally, which has not identified any unexpected safety concerns. The weaknesses of this application have already been enumerated. Given the theoretical risks of hyperfibrinolysis and thromboembolism, as

well as BPAC's recommendation for enhanced surveillance studies for these concerns, OBE agrees with the proposal to require postmarketing studies to assess each of these risks.

The most recent versions of the concept protocols were received on 29 November 2012 and are briefly reviewed here.

ID	LAS-214
Title	"Postmarketing Requirement (PMR) non-interventional 2-armed study to evaluate the safety of OctaplasLG® with special emphasis on monitoring the occurrence of thromboembolic events (TEEs)."
Study Population	<ul style="list-style-type: none"> Patients with Thrombotic Thrombocytopenic Purpura (TTP) undergoing plasma exchange (PEX) procedures from approximately 10-15 sites in North-America and/or continental Europe A minimum of 200 patients (100 per group). The exact sample size is currently under calculation. Inclusion criteria: >18 years of age with definite TTP and thrombocytopenia (platelets < 100 x 10⁹/L) Exclusion criteria: Patients with congenital thrombotic microangiopathies, a history of hypersensitivity to plasma-derived products, known IgA antibodies, severe deficiencies of protein S, patients participating in another clinical treatment study currently or during the past 1 month prior to study inclusion
Timeline	<p>Final study protocol: Aug 2013</p> <p>First patient in: Mar 2014; final patient enrolled: Dec 2017</p> <p>Final study report: July 2018</p>
Objectives	<p>Primary:</p> <ul style="list-style-type: none"> Among TTP patients undergoing PEX, assess the rate of TEEs after OctaplasLG® compared to a matched concurrent control group of patients receiving FFP <p>Secondary:</p> <ul style="list-style-type: none"> Characterize the frequency of TEEs in patients treated with OctaplasLG® and in patients of the concurrent control group receiving FFP by patients' key characteristics Assess the occurrence of (serious) adverse reactions after OctaplasLG® in comparison to FFP
Exposures	<ul style="list-style-type: none"> OctaplasLG® will be given as replacement fluid during PEX. The initial treatment will usually consist of 1.5 plasma volume exchanges for 3 consecutive days, followed by a minimum of 4 and a maximum of 6 single plasma volume exchanges for 4 to 6 days. Subsequent treatment depends upon the patient's response to treatment. The total octaplasLG® volume infused and time details of the infusion(s) will be recorded. FFP will be given as replacement fluid during PEX, following the same schedule as for OctaplasLG®. The total FFP volume used and details of the infusion(s) will be recorded.
Outcomes	<ul style="list-style-type: none"> Main: Thromboembolic events Other safety: Citrate reactions during PEX, plasma-associated adverse reactions, safety laboratory parameters (e.g. troponin), other adverse events. Efficacy: Overall clinical response (4-point rating scale, taking into account platelet count; LDH levels, neurological status).
Covariates and confounding control	<ul style="list-style-type: none"> Laboratory parameters will be assessed as usual at appropriate intervals during the study, and will be documented. Matched pairs approach will be set up to achieve a good match between the two study groups with respect to confounding variables and baseline characteristics, and to avoid bias while ensuring a maximum of statistical power. Patients will be matched by: <ul style="list-style-type: none"> Treatment (OctaplasLG®/FFP) Age groups (18–43 years of age, 44–68 year, >68 years) Sex TEE risk factors
Observation Period	Treatment up to 1 month will be documented. The follow-up period is 4 weeks.
Analysis Plan	Observed incidence rates of TEEs associated with octaplasLG® and FFP respectively will be compared continuously by means of a Maximized Sequential Probability Ratio TEST (MaxSPRT) for Binomial data.

ID	LAS-215
Title	Non-Interventional 2-armed Post-Marketing Requirement (PMR) Study to evaluate the safety of OctaplasLG® versus FFP in patients undergoing orthotopic liver transplantation (LTX) with a special emphasis on hyperfibrinolysis.
Study Population	<ul style="list-style-type: none"> Patients undergoing orthotopic LTX who require management and correction of coagulopathy from approximately 10-20 sites in North-America and/or continental Europe A minimum of 300 patients (140 per group). Sample size calculations will be based upon the expected incidence of clinically relevant hyperfibrinolysis in patients undergoing orthotopic LTX. Gorlinger reported that about 60% of patients undergoing LTX experience hyperfibrinolysis, however, about one third thereof are self-limiting after re-perfusion of the transplant. De Jonge reported hyperfibrinolysis (not defined in more detail) in 6 of 21 (29%) for FFP treated patients and 15 of 20 (75%) for octaplas treated patients. Once the site changed its surgical method, bleeding was no longer an issue. Magner et al. reported fatal cases due to excessive bleeds in 2 of 22 (9%) LTX patients receiving octaplas. In 2008, Octapharma hosted an advisory board meeting with LTX experts. At that meeting the incidence of hyperfibrinolysis was given with 10 to 20%. Inclusion criteria: >18 years of age scheduled to undergo orthotopic LTX, INR >1.5 and MELD score 15-40, who require replacement and substitution of coagulation factors Exclusion criteria: patients with a history of hypersensitivity to plasma-derived products, known IgA antibodies, severe deficiencies of protein S, patients participating in another clinical treatment study currently or during the past 1 month prior to study inclusion
Timeline	Final study protocol: Oct 2013; First patient in: Apr 2014; final patient enrolled: Apr 2017; Final study report: Nov 2017.
Objectives	<p>Primary:</p> <ul style="list-style-type: none"> Among patients undergoing LTX, assess the rate of hyperfibrinolytic events after OctaplasLG® compared to a matched concurrent control group of patients receiving FFP <p>Secondary:</p> <ul style="list-style-type: none"> Characterize the frequency of hyperfibrinolytic events in patients treated with OctaplasLG® and in patients of the concurrent control group receiving FFP by patients' key characteristics Assess the occurrence of (serious) adverse reactions after octaplasLG® in comparison to FFP
Exposures	<ul style="list-style-type: none"> OctaplasLG® will be given during LTX by body weight. Generally a dose of $\geq 10\text{mL/kg}$ can be regarded as clinically relevant dose. The total OctaplasLG® volume infused and time details of the infusion(s) will be recorded. FFP is also dosed based on patient's body weight. Generally a dose of $\geq 10\text{mL/kg}$ can be regarded as clinically relevant. The total FFP volume infused and time details of the infusion(s) will be recorded.
Outcomes	<ul style="list-style-type: none"> "Clinically relevant hyperfibrinolysis" will prospectively be defined, taking into account both clinical and specific laboratory parameters. Proposal (to be discussed with clinical experts): Refractory intraoperative hemorrhages of coagulopathic origin in the presence of mild to moderate abnormalities of standard laboratory indices such as hemoglobin values, platelet count, INR, and aPTT. In addition, increase in d-dimers and fibrin degradation products (FDP), decrease in fibrinogen and $\alpha 2$-antiplasmin levels. Further details with respect to study procedures will be added after consultation of clinical experts.
Covariates and confounding control	<ul style="list-style-type: none"> Matched pairs approach will be set up to achieve a good match between the two study groups with respect to confounding variables and baseline characteristics, and to avoid bias while ensuring a maximum of statistical power. Patients will be matched by: <ul style="list-style-type: none"> Treatment (OctaplasLG®/FFP) Age groups (18–43 years of age, 44–68 year, >68 years) Sex Pre-existing coagulopathies Surgical technique Concomitant use of antifibrinolytic agents Peri-operative use of red blood cell transfusions Indication liver carcinoma
Observation Period	The regular duration of observation for an individual patient will about 2 days (perioperative phase plus 24 hours follow-up).
Analysis Plan	Observed incidence rates of hyperfibrinolytic events associated with octaplasLG® and FFP respectively will be compared continuously by means of a Maximized Sequential Probability Ratio TEST (MaxSPRT) for Binomial data.

7. RECOMMENDATIONS

OBE agrees with the study objectives, methods and timelines proposed in the 2 concept protocols. These 2 targeted safety studies appear to adequately enhance the sponsor's postmarket safety monitoring plan. OBE will review the final study protocols upon submission to FDA.