Fact Sheet for Health Care Professionals or Other Authorized Providers

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of Octapharma's octaplasLG Powder (blood group types A and AB) by U.S. military forces for the emergent treatment of hemorrhage or coagulopathy involving agents of military combat (e.g., firearms, projectiles, and explosive devices) when plasma is not available or when the use of plasma is not practical. This EUA also permits the treatment of other individuals, such as troops, civilians, contractors, and allied military personnel operating with Department of Defense.

What is octaplasLG Powder and why is it needed?

octaplasLG Powder is an unapproved lyophilized form of Octapharma's FDA-approved pooled plasma Octaplas. Octaplas is a solvent/detergent (S/D) treated, pooled human plasma that has been on the global market since 1992 (12.8 million bags sold) with an established safety profile based on substantial post-marketing data. Agents of military combat have the potential to cause imminently life-threatening hemorrhage or coagulopathy in U.S. military personnel. octaplasLG Powder is for use under emergency conditions when plasma is not available or when the use of plasma is not practical. Importantly, octaplasLG Powder does not require refrigeration and is supplied in a form compatible with the logistical constraints of a military operational environment. Given the urgent need for a therapeutic to treat life-threatening hemorrhage and/or coagulopathy under austere combat conditions for U.S. military personnel, the Secretary of Health and Human Services (HHS) has declared that circumstances exist to justify the emergency use of freeze dried plasma for the treatment of hemorrhage or coagulopathy during an emergency involving agents of military combat (e.g., firearms, projectiles, and explosive devices) when plasma is not available for use or when the use of plasma is not practical. Therefore, FDA has issued this EUA to allow access to and use of octaplasLG Powder, an unapproved product. This EUA Fact Sheet provides information about the significant known and potential risks and benefits of the emergency use of octaplasLG Powder.

Controlled clinical studies of octaplasLG Powder have not been performed. Information on safety and effectiveness of octaplasLG Powder is derived from information on safety and effectiveness of Octaplas, and laboratory studies suggesting similar composition and quality of octaplasLG powder (when reconstituted) to Octaplas.

Product Use and Inventory Management

It is expected that U.S. military medical personnel or other Authorized Providers trained in the use of octaplasLG Powder will administer routine standard of care for hemorrhage. This may include, but is not limited to, the following: tourniquets, compression dressings, hemostatic agents, and dressings. If in the opinion of the treating provider, the patient is experiencing life-threatening hemorrhage or coagulopathy, the use of octaplasLG Powder would be appropriate. It is the recipient's choice whether or not to receive octaplasLG Powder. However, it is possible that octaplasLG Powder may be administered in a life-threatening situation where the recipient is not able to make a decision or provide consent.

DoD will distribute the octaplasLG Powder to medical units as needed. The medical units will be responsible for the storage, documentation, and accountability of product usage and will return and warehouse all unused product for final disposition.

The octaplasLG Powder products authorized under FDA EUA are limited to only blood groups A and AB. In the emergency treatment of hemorrhage or coagulopathy, group A and group AB octaplasLG Powder may be used prior to determining the recipient's blood group. Patients should be observed for at least 20 minutes after the administration.

Data Collection

Data collected under this EUA will be used to evaluate the appropriate and safe use of octaplasLG Powder under combat conditions. Record, to the extent practicable given the emergency circumstances, the following whenever octaplasLG Powder is transfused to patients:

- Suspected adverse reactions
- Medication errors associated with the use of the authorized octaplasLG Powder

For the purposes of this EUA, a suspected adverse reaction means any untoward medical occurrence associated with transfusion of octaplasLG Powder for which the healthcare provider believes there is evidence to support that transfusion of octaplasLG Powder caused the untoward medical occurrence. If a suspected adverse reaction is determined to be serious and unexpected, or results in death, report the suspected adverse reaction as soon as reasonably possible according to a process defined by the Department of Defense.

For the purposes of this EUA, serious and unexpected means a reaction that results in death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect, and which is not described under 'Risks and Adverse Events' below.

Adverse events may also be submitted directly to FDA using MedWatch FDA Form 3500 available at http://www.fda.gov/medwatch.

Product Description, Storage Conditions and Product Expiration

octaplasLG Powder is an unapproved lyophilized plasma product created from an FDA-approved pooled plasma product, Octaplas. Octaplas is manufactured from human plasma collected in US licensed plasma donation centers. All plasma donations are tested for relevant transfusion-transmitted infections in accordance with U.S. federal regulations. Octaplas is created from pooled plasma (comprising 370-1,520 individual donations) of single ABO blood groups which undergoes solvent/detergent treatment and nanofiltration. The Octaplas product is then dried using a freeze-drying process to create the octaplasLG Powder. The authorized octaplasLG Powder is of blood groups A and AB. Titers of blood group antibodies were tested in 113 Octaplas batches with blood group A. Mean anti-B antibody titers in blood group A plasma were relatively low, in a range of 4-128. Since the manufacturing processes of Octaplas and octaplasLG Powder are identical, except for the freezing vs. freeze-drying process, similar antibody levels are expected for both products.

- The shelf-life of octaplasLG Powder is 2 years.
- Store between 2°C to 25°C. Stable for 24 months. Do not freeze. Protect from light.
- Reconstituted octaplasLG Powder is stable for 8 hours at standard room temperature (25°C).

- The reconstituted solution should be used immediately if possible and must not be frozen or stored in a refrigerator.
- Significant excursions from the labelled storage conditions should be documented if conditions permit.

Each pack of octaplasLG Powder is packaged as follows:

- 9 - 14 g human plasma protein in a bottle (type I glass), with a stopper (bromobutyl rubber), and a flip-off cap
- 190 ml solvent (water for injections) in a bag
- 1 transfer set
- 2 alcohol swabs
- Transfusion set with filter
- Vented spike adaptor

Global coagulation parameters and specific coagulation factors and inhibitors in octaplasLG Powder compared to Octaplas Pooled Plasma

Parameter	octaplasLG Powder Mean ± standard deviation (n = 3)	Octaplas Mean (min-max) (n = 12)
Activated partial thromboplastin time [sec]	29 ± 2	28 (27-31)
Prothrombin time [sec]	11 ± 0	11.8 (11.2-12.6)
Fibrinogen [mg/ml]	3.1 ± 0.2	3.0 (2.7-3.2)
Coagulation factor II [IU/ml]	0.90 ± 0.00	1.1 (1.0-1.1)
Coagulation factor V [IU/ml]	0.90 ± 0.00	0.9 (0.9-1.0)
Coagulation factor VII [IU/ml]	1.13 ± 0.06	1.1 (1.0-1.2)
Coagulation factor VIII [IU/ml]	0.93 ± 0.12	1.1 (0.8-1.3)
Coagulation factor IX [IU/ml]	1.40 ± 0.10	1.2 (1.0-1.3)
Coagulation factor X [IU/ml]	1.03 ± 0.06	1.1 (1.0-1.1)
Coagulation factor XI [IU/ml]	0.80 ± 0.00	0.9 (0.9-1.0)
Coagulation factor XII [IU/ml]	1.00 ± 0.04	1.2 (1.0-1.4)
Coagulation factor XIII [IU/ml]	0.90 ± 0.02	0.9 (0.9-1.0)
Antithrombin [IU/ml]	1.06 ± 0.05	1.0 (0.9-1.0)
Heparin cofactor II [IU/ml]	1.18 ± 0.06	1.23 ± 0.06
Protein C [IU/ml]	1.03 ± 0.06	1.0 (1.0-1.0)
Protein S [IU/ml]	0.67 ± 0.06	0.7 (0.6-0.8)
Von Willebrand factor ristocetin cofactor activity [IU/ml]	0.95 ± 0.10	0.87 ± 0.08
ADAMTS13[#] activity [IU/ml]	0.92 ± 0.03	1.0 (0.8-1.2)
Plasminogen [IU/ml]	0.86 ± 0.03	0.9 (0.8-0.9)
Plasmin inhibitor[##] [IU/ml]	0.47 ± 0.06	0.4 (0.4-0.5)

[#]A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. Also known as von Willebrand factor-cleaving protease (VWFCP).

[##]Also known as α_2-antiplasmin.

Instructions for Use and Administration

The included transfusion set with a 170-200 µm filter together with the vented spike adaptor should be used for the administration of octaplasLG Powder via intravenous infusion to remove residual particulate matter.

Before reconstitution, both the unopened powder (octaplasLG Powder) and the sterile water for injection (WFI) should be warmed up to room temperature.

The product generally reconstitutes within approximately 15 minutes at room temperature. If the powder is not dissolved within 30 minutes, the product should be discarded.

One vial of octaplasLG Powder contains 9 – 14 g of A or AB blood group specific human plasma proteins. After reconstitution with 190 ml of solvent, the final solution of 200-210 ml contains 45 – 70 mg/ml of A or AB blood group specific human plasma proteins.

The dosage depends on the clinical situation and underlying disorder, but 12-15 ml octaplasLG Powder /kg body weight is a generally accepted starting dose. This should increase the patient's plasma coagulation factor levels by approximately 25%.
Because the protein levels are similar to Octaplas (see table above) octaplasLG Powder can be used the same way as Octaplas.

Reconstitution

1. Reconstitution of octaplasLG Powder should be done at room temperature. Remove the flip-off cap from the powder bottle (octaplasLG Powder) to expose the central portion of the rubber stopper. Disinfect the rubber stopper with an alcohol swab and allow the rubber stopper to dry.

2. Remove the blister from the transfer set and close the clamp on the transfer line.

3. Remove the outer packaging of the WFI bag. Remove the blue protective cap from the bag outlet. Do not touch the rubber stopper of the outlet to maintain sterility.

4. Connect the transfer set to the powder bottle (octaplasLG Powder) by perforating the rubber stopper centrally with the spike. Open the vent next to the spike.

5. Connect the transfer set to the WFI bag by pushing the needle through the blue outlet.

6. Make sure that the transfer set is well connected, hold/hang the WFI bag vertically above the powder bottle and open the clamp. The WFI flows automatically into the powder bottle (octaplasLG Powder). Gently swirl the powder bottle during the WFI transfer.

7. When the transfer is completed remove the spike from the powder bottle and discard the transfer set and the empty WFI bag.

8. Continue to gently swirl the powder bottle until the powder is fully dissolved. Do not shake the bottle to avoid foam formation. In general, the powder should be

dissolved completely within approximately 15 minutes. The reconstituted solution should be clear or slightly opalescent.

9. Examine the glass bottle prior to infusion to ensure the bottle is intact. Do not use a broken bottle under any circumstances.

Product Administration

1. Always use aseptic technique when connecting the transfusion set with the vented spike adaptor and the vial.

2. Remove the blister from the transfusion set and the blister from the vented spike adaptor.

3. Remove the protective cap from the spike of the transfusion set. Slide the vented spike adaptor on the spike of the transfusion set. Then remove the protective cap from the spike of the adaptor.

4. Connect the transfusion set with the adaptor to the powder bottle (octaplasLG Powder) by perforating the rubber stopper centrally with the spike of the adaptor.

5. Ensure the spike is fully inserted into the vial so that liquid can flow through the tubing.

6. Gently squeeze the drip chamber of the transfusion set to fill it partially with liquid.

7. Transfuse the product according to your established clinical protocols. Patients' vital signs should be closely monitored throughout the infusion as conditions permit.

8. Repeat administration as medically necessary.

Use in Specific Populations

Pediatric Use:

Octaplas was evaluated in 91 pediatric patients (age range 0-20 years) in two post-marketing requirement studies. Patients were dosed based on body weight and doses were adjusted as needed. There were no hyperfibrinolytic or treatment-related thromboembolic events reported by investigators.

Pregnancy:

Animal reproduction studies have not been conducted with Octaplas. It is not known whether Octaplas can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Octaplas should be given to a pregnant woman only if clearly needed.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Geriatric Use:

Clinical studies of Octaplas did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Other reported

clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Risks and Adverse Events

- Transfusion reactions (e.g., severe hypotension, anaphylactic shock) can occur with administration of any blood derived product. Closely monitor patient status during infusion for signs of a reaction. If a reaction occurs, stop the infusion immediately and treat the symptoms as appropriate.
- High infusion rates can induce hypervolemia with subsequent pulmonary edema or heart failure.
- Excessive bleeding due to hyperfibrinolysis can occur due to low levels of alpha 2-antiplasmin.
- Thrombosis can occur due to low levels of Protein S.
- octaplasLG Powder is made from human blood and may carry the risk of transmitting infectious agents, e.g., viruses and theoretically, the variant Creutzfeldt-Jakob disease and Creutzfeldt-Jakob disease agent.
- Hemolytic reactions due to ABO incompatibility
- Citrate toxicity can cause a decreased ionized calcium caused by the presence in the circulation of large quantities of citrate anticoagulant. Citrate toxicity can occur when the infusion rate and volume exceed one milliliter of octaplasLG Powder per kg per minute. The octaplasLG Powder infusion rate should not exceed 0.020-0.025 mmol citrate per kilogram per minute (i.e., less than one milliliter octaplasLG Powder per kg per minute). Symptoms attributable to citrate toxicity (hypocalcemia) include fatigue, paresthesia and muscle spasms, especially in patients with liver function disorders. Calcium may be administered to treat citrate toxicity.
- Transfusion-related acute lung injury has been reported spontaneously in patients receiving octaplasLG and other blood products.

Contraindications

- IgA deficiency
- Severe deficiency of Protein S
- History of hypersensitivity to fresh frozen plasma (FFP) or to plasma-derived products including any plasma protein
- History of hypersensitivity reaction to Octaplas/octaplasLG Powder

Risk Benefit Statement

Data obtained from clinical trials demonstrate that Octaplas is non-inferior to fresh frozen plasma (FFP) in the treatment of hemorrhage and coagulopathy. octaplasLG Powder is a lyophilized form of Octaplas that has been shown to have a similar biochemical profile to Octaplas. It is expected octaplasLG Powder will maintain a similar safety profile as Octaplas. In contrast to Octaplas and plasma components, the lower logistical requirements of octaplasLG Powder allow it to be delivered to patients in environments where plasma is not available or when the use of plasma is not practical. Therefore, in these cases of life-threatening hemorrhage and/or coagulopathy FDA has concluded that that the known and

potential benefits of octaplasLG Powder, when used in accordance with the scope of authorization, outweigh the known and potential risks.

Alternative treatment options

Plasma transfusions are primarily used for the emergent treatment of hemorrhage or coagulopathy. Plasma products available for transfusion include the plasma components described in the AABB Circular of Information or Octaplas solvent-detergent treated plasma. Other replacement strategies can also be considered depending on the underlying condition; these include whole blood, packed red blood cells, platelets, prothrombin complex concentrate, fibrinogen concentrate and human albumin. octaplasLG Powder is for use when other plasma products are not available, or their use is not practical.

Contact information for reporting adverse events and additional information about the product

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.