Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

LG-octaplas powder and solvent for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LG-octaplas is presented as a powder and solvent for solution for infusion. One vial contains 9 - 14 g of ABO-blood group specific human plasma proteins. After reconstitution with 190 ml of solvent, the solution contains 45 - 70 mg/mL ABO-blood group specific human plasma proteins. LG-octaplas is supplied in separate presentations according to the following blood groups:
Blood group A
Blood group B
Blood group AB
Blood group O
For details about important coagulation factors and inhibitors, see section 5.1 and table 2.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.
The powder is friable solid of almost white or slightly yellow colour.
The solvent is a clear and colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Complex deficiencies of coagulation factors such as coagulopathy due to severe hepatic failure or massive transfusion.
- Substitution therapy in coagulation factor deficiencies, when a specific coagulation factor concentrate (e.g. factor V or factor XI) is not available for use or in emergency situations when a precise laboratory diagnosis is not possible.
- Rapid reversal of the effects of oral anticoagulants (coumarin or indanedione type) when a prothrombin complex concentrate is not available for use, or administration of vitamin K is insufficient due to impaired liver function or in emergency situations.
- Potentially dangerous haemorrhages during fibrinolytic therapy, using e.g. tissue plasminogen activators, in patients who fail to respond to conventional measures.
- Therapeutic plasma exchange procedures, including those in thrombotic thrombocytopenic purpura (TTP).

4.2 Posology and method of administration

Posology:
The dosage depends upon the clinical situation and underlying disorder, but 12-15 ml LG-octaplas/kg body weight is a generally accepted starting dose. This should increase the patient's plasma coagulation factor levels by approximately 25%.
It is important to monitor the response, both clinically and with measurement of e.g. activated partial thromboplastin time (aPTT), prothrombin time (PT), and/or specific coagulation factor assays.

Dosage for coagulation factor deficiencies:
An adequate haemostatic effect in minor and moderate haemorrhages or surgery in coagulation factor deficient patients is normally achieved after the infusion of 5-20 mL LG-octaplas/kg body weight. This should increase the patient's plasma coagulation factor levels by approximately 10-33 %. In the event of major haemorrhage or surgery, the expert advice of a haematologist should be sought.

Dosage for TTP and haemorrhages in intensive plasma exchange:
For therapeutic plasma exchange procedures, the expert advice of a haematologist should be sought.
In TTP patients the whole plasma volume exchanged should be replaced with LG-octaplas.

Method of administration

Administration of LG-octaplas must be based on ABO-blood group specificity. In emergency cases, LG-octaplas blood group AB can be regarded as universal plasma since it can be given to all patients regardless of blood group.

LG-octaplas must be administered by intravenous infusion after reconstitution, as described in section 6.6, using a vented infusion set with a filter. An aseptic technique must be used throughout the infusion.

The reconstituted solution is clear to slightly opalescent. Citrate toxicity can occur when more than 0.020-0.025 mmol citrate per kg per minute is administered. Therefore, the infusion rate should not exceed 1 mL of LG-octaplas per kg per minute. Toxic effects of citrate can be minimised by giving calcium gluconate intravenously into another vein.

The reconstituted product should be administered at tolerable temperature to prevent hypothermia but not above 37°C.

Paediatric population

There is limited data in children and adolescents (0-16 years) (see section 4.4, 4.8 and 5.1).

4.3 Contraindications

- IgA deficiency with documented antibodies against IgA
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or residues from the manufacturing process, as stated in section 5.3.
- Severe deficiencies of protein S

4.4 Special warnings and precautions for use

LG-octaplas should not be used:

- As a volume expander.
- In cases of bleeding caused by coagulation factor deficiencies where a specific factor concentrate is available for use.
- To correct hyperfibrinolysis in liver transplantation or other conditions with complex disturbances of haemostasis caused by a deficiency of plasmin inhibitor, also named α_2-antiplasmin.

LG-octaplas should be used with caution under the following conditions:

- IgA deficiency.
- Plasma protein allergy.
- Previous reactions to fresh-frozen plasma (FFP) or solvent/detergent treated plasma (including LG-octaplas).
- Manifest or latent cardiac decompensation.
- Pulmonary oedema.

In order to reduce the risk for venous thromboembolism caused by the reduced protein S activity of LG-octaplas compared to normal plasma (see section 5.1), caution should be exercised and appropriate measures should be considered in all patients at risk for thrombotic complications.

In intensive plasma exchange procedures, LG-octaplas should only be used to correct the coagulation abnormality when abnormal haemorrhage occurs.

Viral safety

Standard measures to prevent infections resulting from the use of medical products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pool for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown and emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV. The measures taken may be of limited value against non-enveloped virus such as HAV, HEV and Parvovirus B19.

Parvovirus B19 infection may be serious for pregnant woman (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia). HEV may also seriously affect seronegative pregnant women. Therefore LG-octaplas should only be administered to these patients if strongly indicated.

Appropriate vaccination (e.g. against HBV and HAV) for patients in regular receipt of medicinal products derived from human blood or plasma should be considered.

Additionally, a step to remove prions is incorporated.

Blood group-specific administration
Administration of LG-octaplas must be based on ABO-blood group specificity. In emergency cases, LG-octaplas blood group AB can be regarded as universal plasma since it can be given to all patients regardless of blood group.
Patients should be observed for at least 20 minutes after the administration.
Anaphylactic reactions
In case of anaphylactic reaction or shock, the infusion must be stopped immediately. Treatment should follow the guidelines for shock therapy.
Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
Paediatric population
Some cases of hypocalcaemia, possibly caused by citrate binding, have been observed during therapeutic plasma exchange in the paediatric population (see section 4.8). Monitoring of ionized calcium is recommended during such use of octaplasLG.
Interference with serological testing
Passive transmission of plasma components from LG-octaplas (e.g. β-human chorionic gonadotropin; β-HCG) may result in misleading laboratory results in the recipient. For example, a false-positive pregnancy test result has been reported following passive transmission of β-HCG.

This medicinal product contains maximum 920 mg sodium per bottle, equivalent to maximum 46% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions:
No interactions with other drugs have been identified.
Incompatibilities:

- LG-octaplas product can be mixed with red blood cells and platelets if ABO compatibility of both preparations is respected.
- LG-octaplas must not be mixed with other medicinal products, as inactivation and precipitation may occur.
- To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as LG-octaplas.

4.6 Fertility, pregnancy and lactation

The safety of LG-octaplas for use in human pregnancy has not been established in controlled clinical trials. It is not known whether LG-octaplas can affect reproduction capacity. The product should be administered to a pregnant or lactating woman only if alternative therapies are regarded inappropriate.
For potential risk of Parvovirus B19 and HEV transmission, see section 4.4.

4.7 Effects on ability to drive and use machines

After ambulant infusion, the patient should rest for one hour.
LG-octaplas has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Hypersensitivity reactions may rarely be observed. These are usually mild allergic type reactions consisting of localised or generalised urticaria, erythema, flushing and pruritus. More severe forms can be complicated by hypotension or angioedema of the face or larynx. If other organ systems – cardiovascular, respiratory or gastrointestinal – are involved, the reaction would be considered anaphylactic or anaphylactoid. Anaphylactic reactions may have a rapid onset and may be serious; the symptom complex may include hypotension, tachycardia, bronchospasm, wheezing, coughing, dyspnoea, nausea, vomiting, diarrhoea, abdominal or back pain. Severe reactions may proceed to shock, syncope, respiratory failure and very rarely even death.

High infusion rates may rarely cause cardiovascular effects as a result of citrate toxicity (fall in ionised calcium), especially in patients with liver function disorders. In the course of plasma exchange procedures, symptoms attributable to citrate toxicity such as fatigue, paraesthesia, tremor, and hypocalcemia may be observed rarely.

During clinical trials with LG-octaplas and its predecessor product octaplas, and their post-approval use, the following adverse reactions have been identified:

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse reactions that have been identified for LG-Octaplas

System organ class*	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
Blood and lymphatic system disorders				haemolytic anaemia haemorrhagic diathesis
Immune system disorders		anaphylactoid reaction	hypersensitivity	anaphylactic shock anaphylactic reaction
Psychiatric disorders				anxiety agitation restlessness
Nervous system disorders		hypoesthesia		dizziness paraesthesia
Cardiac disorders				cardiac arrest arrhythmia tachycardia
Vascular disorders				thromboembolism (LLT) hypotension hypertension circulatory collapse flushing
Respiratory, thoracic and mediastinal disorders		hypoxia		respiratory failure pulmonary haemorrhage bronchospasm pulmonary oedema dyspnoea respiratory disorder
Gastrointestinal disorders		vomiting nausea		abdominal pain
Skin and subcutaneous tissue disorders	urticaria pruritus			rash (erythematous) hyperhidrosis
Musculoskeletal and connective tissue disorders				back pain
General disorders and administration site conditions		pyrexia		chest pain chest discomfort chills localised oedema malaise application site reaction
Investigations				antibody test positive oxygen saturation decreased
Injury, poisoning and procedural complications				transfusion-related circulatory overload citrate toxicity haemolytic transfusion reaction

*This table contains MedDRA Preferred Terms (PTs) unless indicated otherwise.
LLT, MedDRA Lowest Level Term

Paediatric population
In the course of plasma exchange procedures, hypocalcaemia may be observed in the paediatric population especially in patients with liver function disorders or in case of high infusion rates. Monitoring of ionized calcium (see section 4.4) is recommended during such use of octaplasLG (see section 4.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

- High dosages or infusion rates may induce hypervolaemia/circulatory overload, pulmonary oedema and/or cardiac failure.
- High infusion rates may cause cardiovascular effects as a result of citrate toxicity (fall in ionised calcium), especially in patients with liver function disorders.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitutes and plasma protein fractions,
ATC code: B05A A.
The content and distribution of plasma proteins in LG-octaplas remain in the final product at comparable levels to those in the raw material FFP, i.e. 45-70 mg/mL, and the major plasma proteins are all within the reference ranges for healthy blood donors (see table 2). Out of a mean total protein content of 55 mg/ml, albumin accounts for 55% (31 mg/ml), whereas the immunoglobulin classes G, A, and M are present at levels of 6.9, 1.4, and 0.4 mg/ml, respectively. As a result of the S/D treatment and purification, the content in lipids and lipoproteins is reduced. This is of no relevance within the indications for LG-octaplas.
The manufacturing process levels out inter-donor variations and maintain the plasma proteins in a functional state. Therefore, LG-octaplas possesses the same clinical activity as the average single-donor FFP unit but is more standardised. The finished product is tested for coagulation factors V, VIII, and XI, and the inhibitors protein C, protein S, and plasmin inhibitor. A minimum of 0.5 IU/mL is obtained for each of the three coagulation factors, whereas the inhibitor levels are guaranteed equal or higher than 0.7, 0.3, and 0.2 IU/mL. The fibrinogen content is between 1.5 and 4.0 mg/mL. In routine production, all clinically important parameters are within the 2.5-97.5 percentiles reference range for single-donor FFP, except plasmin inhibitor (also known as α_2-antiplasmin) that is just below (see table 2). LG-octaplas displays the same von Willebrand factor multimeric pattern as normal plasma.

Table 2: Global coagulation parameters and specific coagulation factors and inhibitors in LG-octaplas

Parameter	**LG-octaplas Mean ± standard deviation (n = 3)**	**Reference range***
Activated partial thromboplastin time [sec]	29 ± 2	28-41
Prothrombin time [sec]	11 ± 0	10-14**
Fibrinogen [mg/mL]	3.1 ± 0.2	1.5-4.0**
Coagulation factor II [IU/mL]	0.90 ± 0.00	0.65-1.54
Coagulation factor V [IU/mL]	0.90 ± 0.00	0.54-1.45
Coagulation factor VII [IU/mL]	1.13 ± 0.06	0.62-1.65
Coagulation factor VIII [IU/mL]	0.93 ± 0.12	0.45-1.68
Coagulation factor IX [IU/mL]	1.40 ± 0.10	0.45-1.48
Coagulation factor X [IU/mL]	1.03 ± 0.06	0.68-1.48
Coagulation factor XI [IU/mL]	0.80 ± 0.00	0.42-1.44
Coagulation factor XII [IU/mL]	1.00 ± 0.04	0.40-1.52
Coagulation factor XIII [IU/mL]	0.90 ± 0.02	0.65-1.65
Antithrombin [IU/mL]	1.06 ± 0.05	0.72-1.45
Heparin cofactor II [IU/mL]	1.18 ± 0.06	0.65-1.35
Protein C [IU/mL]	1.03 ± 0.06	0.58-1.64
Protein S [IU/mL]	0.67 ± 0.06	0.56-1.68

Von Willebrand factor ristocetin cofactor activity [IU/mL]	0.95 ± 0.10	0.45-1.75
ADAMTS13[#] activity [IU/mL]	0.92 ± 0.03	0.50-1.10**
Plasminogen [IU/mL]	0.86 ± 0.03	0.68-1.44
Plasmin inhibitor[##] [IU/mL]	0.47 ± 0.06	0.72-1.32

*According [1,2] based on the testing of 100 healthy blood donors and defined by the 2.5 and 97.5 percentiles; or **according package insert of test kit.
[#]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.

Clinical studies:
An open-label, multicentre, post-marketing study investigated the safety, tolerability, and efficacy of LG-octaplas in 37 neonates/infants (0 to 2 years old), and 13 children and adolescents (>2 to 16 years old). Forty patients had cardiac surgery, 5 an orthotopic liver transplant, and 5 required replacement of multiple coagulation factors (4 of these patients had sepsis). In the 28 patients who had bypass priming (all aged ≤2 years), the mean dose was 20.2 mL/kg. In 20 other patients, the mean dose of the first infusion was 16.5 mL/kg in those aged ≤2 years and 12.7 mL/kg in those aged >2 years. There were no hyperfibrinolytic events or thromboembolic events reported that were judged to be related to treatment with LG-octaplas. Results of the haemostatic tests performed following infusions of LG-octaplas were within the ranges expected by the investigators for patients requiring plasma infusions for bleeding indications.

5.2 Pharmacokinetic properties

LG-octaplas has similar pharmacokinetic properties as FFP.

[1] Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and characterization of a solvent/detergent-treated human plasma. Vox Sang 1992; 63:178-185
[2] Beeck H, Hellstern P. In vitro characterization of solvent/detergent-treated human plasma and of quarantine fresh frozen plasma. Vox Sang 1998; 74 (Suppl. I):219-223

5.3 Preclinical safety data

Virus inactivation is carried out using Tri (N-Butyl) Phosphate (TNBP) and Octoxynol (Triton X-100). These S/D reagents are removed during the purification process. The maximum amounts of TNBP and Octoxynol in the finished product < 2 µg/ml and < 5 µg/ml, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium dihydrogenphosphate dihydrate
Citric acid monohydrate
Phosphoric acid
Glycine

Solvent:
Water for injections

6.2 Incompatibilities

- LG-octaplas product can be mixed with red blood cells and platelets if ABO compatibility of both preparations is respected.
- LG-octaplas must not be mixed with other medicinal products, as inactivation and precipitation may occur.
- To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as LG-octaplas.

6.3 Shelf life

2 years

The chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at room temperature (max. +25°C). From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions are the responsibility of the user.
The reconstituted solution must not be frozen or stored in a refrigerator.
Partially used bottles should be discarded.

6.4 Special precautions for storage

Do not store above +25°C.
Do not freeze.
Protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each package of LG-octaplas contains:
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
Pack size of 1.

6.6 Special precautions for disposal and other handling

Do not use after the expiry date given on the label.
Do not re-transfer the reconstituted product back to the WFI bag.
Check all components (bottle, transfer set, bag) for damage prior to use. Do not use damaged components.

Instructions for use and handling and disposal
Please read all the instructions and follow them carefully!
During the procedure described below, aseptic technique must be maintained!
Before reconstution both the powder (LG-octaplas) and the solvent (WFI) should be warmed in unopened containers 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.

Reconstitution

1. Reconstitution of LG-octaplas should be done at room temperature. Remove the flip-off cap from the powder bottle (LG-octaplas) 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 (LG-octaplas) by perforating the rubber stopper centrally with the spike. Open the valve 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 (LG-octaplas). Start with gently swirling of 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 with gently swirling of 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. LG-octaplas must be administered by intravenous infusion using a vented infusion set with a filter to remove potential residual particulate matters. Commercially available vented infusion sets for blood product transfusion with integrated filter of 170-200 µm pore size can be used.

For further details on administration of the reconstituted product see section 4.2 (Method of administration).
For storage conditions after reconstitution of the medicinal product, see section 6.3.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Octapharma (IP) SPRL
Allée de la Recherche 65
1070 Anderlecht
Belgium

8 MARKETING AUTHORISATION NUMBER

PA2219/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th March 2023

10 DATE OF REVISION OF THE TEXT