Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

LG-octaplas, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A 200 ml bag contains 9 - 14 g of ABO-blood group specific human plasma proteins (45 - 70 mg/mL). 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

Solution for infusion.
The frozen solution is (slightly) yellow.

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 thawing, as described in section 6.6, using an infusion set with a filter. An aseptic technique must be used throughout the infusion.
After thawing the solution is clear to slightly opalescent and free of solid or gelatinous particles.
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.

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 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.
It is strongly recommended that every time that LG-octaplas is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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 bag, 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 interactions

Interactions:
No interactions with other drugs have been identified.

Incompatibilities:
• LG-octaplasproduct 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 predecessor product, and its 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 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		hypoaesthesia		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 bronchspasm 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		pyrexia		chest pain

disorders and administration site conditions				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 hypocalcemia 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 58 mg/ml, albumin accounts for 50% (29 mg/ml), whereas the immunoglobulin classes G, A, and M are present at levels of 8.1, 1.6, and 0.8 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 α2-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 = 5)**	**Reference range***
Activated partial thromboplastin time [sec]	30 ± 1	28-41
Prothrombin time [sec]	11 ± 0	10-14**
Fibrinogen [mg/mL]	2.6 ± 0.1	1.5-4.0**
Coagulation factor II [IU/mL]	1.01 ± 0.07	0.65-1.54
Coagulation factor V [IU/mL]	0.76 ± 0.05	0.54-1.45
Coagulation factor VII [IU/mL]	1.09 ± 0.05	0.62-1.65
Coagulation factor VIII [IU/mL]	0.80 ± 0.07	0.45-1.68
Coagulation factor IX [IU/mL]	0.88 ± 0.10	0.45-1.48
Coagulation factor X [IU/mL]	0.99 ± 0.05	0.68-1.48
Coagulation factor XI [IU/mL]	0.88 ± 0.04	0.42-1.44
Coagulation factor XII [IU/mL]	1.04 ± 0.08	0.40-1.52
Coagulation factor XIII [IU/mL]	1.03 ± 0.06	0.65-1.65
Antithrombin [IU/mL]	0.86 ± 0.11	0.72-1.45
Heparin cofactor II [IU/mL]	1.12 ± 0.05	0.65-1.35
Protein C [IU/mL]	0.86 ± 0.08	0.58-1.64
Protein S [IU/mL]	0.63 ± 0.08	0.56-1.68
Von Willebrand factor ristocetin cofactor activity [IU/mL]	0.93 ± 0.08	0.45-1.75
ADAMTS13# activity [IU/mL]	1.13 ± 0.17	0.50-1.10**
Plasminogen [IU/mL]	0.84 ± 0.06	0.68-1.44
Plasmin inhibitor## [IU/mL]	0.61 ± 0.04	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 a2-antiplasmin.

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[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

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.

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 are < 2 microg/ml and <5 microg/ml, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Sodium dihydrogenphosphate dihydrate
Glycine

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

4 years.
After thawing, chemical and physical in-use stability has been demonstrated for 5 days at 2-8°C or 8 hours at room temperature (20-25°C).
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store and transport frozen (at ≤ -18°C).
Store in the original package in order to protect from light.

6.5 Nature and contents of container

200 ml of ABO-blood group specific human plasma proteins in bag (polyvinyl chloride) over-wrapped with a film.
Pack size of 1 and 10.

6.6 Special precautions for disposal and other handling

Do not use after the expiry date given on the label.

There are several options for thawing frozen LG-octaplas:

- Water bath:

Thaw in the outer wrapper for not less than 30 minutes in a circulating water bath at +30°C to +37°C. An overwrap bag may be used to provide further protection of contents if appropriate.
Prevent water from contaminating the entry port. The minimum thawing time is 30 minutes at 37°C. Temperature in the water bath must never exceed +37 °C and should not be lower than +30 °C.
The thawing time depends on the number of bags in the water bath. If more plasma bags are thawed in parallel, the thawing time can be prolonged, but should not be longer than 60 minutes.

- Using a dry tempering system such as the SAHARA-III:

Place the LG-octaplas bags on the agitation plate according to the manufacturer instructions and thaw plasma using the fast tempering function. When a +37°C blood component temperature is indicated on the temperature display, terminate the tempering process and remove the bags.
During thawing of LG-octaplas using a dry tempering system, it is recommended to use the protocol printer to record the course of the blood component temperature and error messages in event of failure.

- Others:

Other thawing systems for frozen LG-octaplas can be used on the condition that the methods are validated for that purpose.
Allow the content of the bag to warm to approximately +37 °C before infusion. The temperature of LG-octaplas must not exceed +37 °C. Remove the outer wrapper and examine the bag for cracks or leaks.
Avoid shaking.
After thawing the solution is clear to slightly opalescent and free of solid or gelatinous particles.
Do not use solutions which are cloudy or have deposits and/or discoloration.
Thawed LG-octaplas must not be refrozen. Unused product must be discarded.
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

PA2219/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th March 2001
Date of last renewal: 4th March 2013

10 DATE OF REVISION OF THE TEXT

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