LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# octaplasLG, powder and solvent for infusion (plasma protein, human)

# SE/H/1866/02/DC

**This module reflects the scientific discussion for the approval of octaplasLG. The procedure was finalised on 2023-02-01. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for octaplasLG, Powder and solvent for solution for infusion.

The active substance is plasma protein, human, Octapharma EMEA/H/PMF/000008/05. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, pharmaceutical form, of the previously authorised product octaplasLG 45-70 mg/ml, solution for infusion marketed by Octapharma AB since 2000 in SE. Please note that a Public Assessment Report is not available for octaplasLG, solution for infusion of previously authorised product.

The application for octaplasLG , 45-70 mg/ml, powder and solvent for solution for infusion, is an application submitted according to Article 8(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CZ, DK, ES, FI, FR, HR, HU, IE, LU, MT, NL, NO, XI(UK) as concerned member states (CMS).

**Potential similarity with orphan medicinal products**

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

OctaplasLG is a freeze dried powder and solution product that is analogous to OctaplasLG, which has been in the market since 2009. The applicant states that biochemical comparability has been shown for OctaplasLG and OctaplasLG, solution for infusion .

The applicant also states that standard non-clinical studies investigating pharmacodynamics and toxicity have not been performed since administration of human plasma to animals would lead to immune reactions making assessments impossible.

The applicant finally concludes, that since the reconstituted OctaplasLG is biochemical identical to OctaplasLG, solution for infusion non-clinical studies are not considered necessary, and that module 2.4 of OctaplasLG applies to OctaplasLG .

Given that OctaplasLG is a human plasma product, the applicants approach to not perform any non-clinical studies is acceptable.

**Environmental Risk Assessment (ERA)**

An ERA has been submitted for the excipients Tri-n-butyl phosphate (TNBP) and Octoxynol (Triton X-100) which are used for S/D process to inactivate viruses during the manufacturing of OctaplasLG .

The applicant stipulates that residual amounts of TNBP and Triton X-100 are estimated to reach a maximum level of 2 ppm and 5 ppm, respectively. The submitted ERA contains calculated PEC values for TNBP and Triton X-100 of 2,9 x 10-8 µg/L and 1,1x10-4 µg/L, respectively. Since theses values are below the action limit of 0,01 µg/L the applicant concludes that an environmental risk is unlikely.

The applicant also provides calculated log Kow values that were <4.5 for both detergents plus an experimental log Kow value for TNBP at 2.5-4.

In addition, the applicant states that none of substances are known endocrine disruptors.

The applicant has provided an ERA up to Phase I for the two excipients (TNBP and Triton X-100). This is not considered necessary for excipients which, unless pre-established toxic to the environment, generally do not require such an assessment (especially excipients that are present at low ppm levels in the product). As such, no deeper assessment of the presented Phase I will be conducted. It can be noted though, for future reference, that the default approach for Log Kow data is the submission of high-quality experimental studies and that in-silico calculations are generally not considered relevant. PEC calculation based on consumption data are also not generally considered relevant.

The human protein component of OctaplasLG is not within the scope of EMA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1)

# IV. CLINICAL ASPECTS

**Pharmacokinetics**

No new pharmacokinetic studies have been provided, and none are considered required, provided that the pharmaceutical characterisation demonstrates essentially similar coagulation factor levels and activities as OctaplasLG.

**Pharmacodynamics**

The product is expected to provide similar activity of the full range of coagulation factors in comparison to OctaplasLG.

**Clinical efficacy**

No new efficacy studies have been provided, and none are considered required, provided that the pharmaceutical characterisation demonstrates essentially similar coagulation factor levels and activities as OctaplasLG. No clinically relevant differences have been identified (please see Table 1 and 2 below).

**Table 1: Quality test parameters for product release**

| Parameters | Ph. Eur. Specifications | Acceptance criterion [2] | OctaplasLG PPQ batches | | | Octaplas LG validation [3] | Octaplas LG routine batches [4] |
|---|---|---|---|---|---|---|---|
| | | | M049A942 US | M051D942 US | M102A942 US | | |
| Visual control | An almost white or slightly yellow powder or friable solid | | Conform | Conform | Conform | Conform | Conform |
| Protein composition | Corresponds to the pattern of normal human plasma | | Conform | Conform | Conform | Conform | Conform |
| Haemagglutinins | Corresponds to the blood group stated on the label | | Conform | Conform | Conform | Conform | Conform |
| pH value | 6.5 – 7.6 | 7.0-7.6 | 7.5 | 7.6 | 7.4 | 7.0 – 7.2 | 7.2 – 7.6 |
| Solubility | Not specified | within 30 min at +20°C to +25°C | 14 min | 12 min | 15 min | N/A | N/A |
| | The filtered plasma solution is clear to slightly opalescent and free of solid or gelatinous particles | | Conform | Conform | Conform | | |
| Osmolality [mOsmol/kg] | ≥ 240 | 320 – 420 | 332 | 335 | 331 | 370 – 391 | 345 – 352 |
| Total protein [mg/mL] | ≥ 45 | 45 – 70 | 55 | 56 | 55 | 56 – 60 | 54 – 62 |
| Activated coagulation factors or NaPTT [sec] | ≥ 150 | ≥ 150 | 377 | 368 | 461 | 246 – 274 | 237 – 385 |
| HAV-Ab [IU/mL] | ≥ 1 | ≥ 0.3 | 3.1 | 1.8 | 1.7 | 1.3 – 2.7 | 1.4 – 3.8 |
| Irregular erythrocyte antibodies | No irregular erythrocyte antibodies | | Conform | Conform | Conform | Conform | Conform |
| Citrate [mmol/L] | ≤ 25 | 10 – 25 | 20 | 20 | 22 | 19 – 20 | 15 – 17 |
| Calcium [mmol/L] | ≤ 5.0 | ≤ 5.0 | 1.9 | 1.9 | 1.8 | 0.8 | 1.7 – 1.9 |
| Potassium [mmol/L] | ≤ 5.0 | ≤ 5.0 | 3.4 | 3.5 | 3.4 | 3.1 – 3.3 | 3.2 – 3.8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Sodium [mmol/L] | ≤ 200 | ≤ 200 | 159 | 163 | 160 | 160 – 163 | 156 – 179 |
| Water [% (w/w)] | * | ≤ 2.0 | 0.3 | 0.3 | 0.4 | N/A | N/A |
| Sterility | Sterile | Sterile | Approved | Approved | Approved | Approved | Approved |
| Pyrogens | Free of pyrogens | Free of pyrogens | Approved | Approved | Approved | Approved | Approved |
| Factor V [IU/mL] | ≥ 0.5 | ≥ 0.5 | 0.9 | 0.9 | 0.9 | 0.6 – 0.7 | 0.9 – 1.0 |
| Factor VIII [IU/mL] | ≥ 0.5 | ≥ 0.5 | 0.8 | 1.0 | 1.0 | 0.6 – 0.7 | 0.8 – 1.3 |
| Factor XI [IU/mL] | ≥ 0.5 | ≥ 0.5 | 0.8 | 0.8 | 0.8 | 0.8 – 0.9 | 0.9 – 1.0 |
| Protein C [IU/mL] | ≥ 0.7 | ≥ 0.7 | 1.0 | 1.0 | 1.1 | 0.9 | 1.0 |
| Protein S [IU/mL] | * | ≥ 0.3 | 0.7 | 0.6 | 0.7 | 0.4 – 0.5 | 0.6 – 0.8 |
| Plasmin inhibitor [U/mL] | * | ≥ 0.2 | 0.4 | 0.5 | 0.5 | 0.4 – 0.5 | 0.4 – 0.5 |
| Confidence limits Factor V [%] | Within 80 – 120 | | 98 – 102 | 98 – 102 | 97 – 103 | N/A | 96 – 104 |
| Confidence limits Factor VIII [%] | Within 80 – 120 | | 96 – 104 | 96 – 105 | 95 – 105 | N/A | 94 – 107 |
| Confidence limits Protein C [%] | Within 80 – 120 | | 99 – 101 | 99 – 101 | 99 – 101 | N/A | 96 – 104 |
| Confidence limits Protein S [%] | Within 80 – 120 | | 96 – 104 | 95 – 105 | 96 – 104 | N/A | 90 – 111 |
| Confidence limits Plasmin inhibitor [%] | Within 80 – 120 | | 97 – 103 | 96 – 104 | 98 – 102 | N/A | 96 – 104 |
| Confidence limits Factor XI [%] | Within 80 – 125 | | 97 - 103 | 95 - 105 | 93 - 108 | N/A | 92 – 109 |
| aPTT [sec] | Not specified | 23 – 40 | 31 | 29 | 28 | 30 – 34 | 27 – 31 |
| Phosphate [mmol/L] | Not specified | 2.0 – 7.5 | 5.2 | 5.1 | 5.5 | 5.4 – 5.7 | 3.0 – 3.7 |
| Glycine [mg/mL] | Not specified | 4.0 – 6.0 | 5.1 | 5.6 | 5.0 | 4.0 – 5.1 | 4.3 – 5.3 |
| TNBP [µg/mL] | < 2 | < 2 | < 1 | < 1 | < 1 | < 0.5 | < 1 |
| Octoxynol [µg/mL] | < 5 | < 5 | < 1 | < 1 | < 1 | < 1.0 | < 1 |
| Fibrinogen [mg/mL] | Not specified | 2.4 – 3.6 | 3.1 | 2.9 | 3.2 | 2.8 – 3.2 | 2.7 – 3.2 |

**Table 2: Additional parameters.** Results in *OctaplasLG* PPQ batches were compared with the results of *OctaplasLG* validation batches, *OctaplasLG* routine batches as well as reference ranges for normal plasma.

| Parameters | Reference ranges [5] | OctaplasLG PPQ batches | | | OctaplasLG validation (n=3) [6] | OctaplasLG routine batches (n=12) [4] |
|---|---|---|---|---|---|---|
| | | M049A942US | M051D942US | M102A942US | | |
| Global coagulation parameters | | | | | | |
| aPTT [sec] | 28 – 40 | 31 | 29 | 28 | 30 – 34 | 27 – 31 |
| PT [sec] | 12.5 – 16.1 | 11.4 | 11.4 | 11.5 | 11.4 – 11.6 | 11.2 – 12.6 |
| RT [sec] | < 20 | 14.3 | 14.3 | 13.1 | 16.9 – 20.9 | 14.2 – 14.9 |
| TT [sec] | 14 – 20 | 12.8 | 12.2 | 12.1 | 14.5 – 15.2 | 13.9 – 16.6 |
| Fibrinogen [mg/mL] | 1.45 – 3.85 | 3.1 | 2.9 | 3.2 | 2.8 – 3.2 | 2.7 – 3.2 |
| TGA:<br>Thrombin [nM]<br>Lag phase [min]<br>AUC [nM x min] | n.d. | <br>452<br>10.7<br>3,873 | <br>474<br>10.7<br>4,007 | <br>472<br>10.7<br>4,008 | <br>407 – 413<br>12.4 – 13.3<br>3,997 – 4,046 | <br>496 – 572<br>10.0 – 12.0<br>3,924 – 4,272 |
| Coagulation factors and proteins of the haemostatic system | | | | | | |
| Factor II [IU/mL] | 0.65 – 1.54 | 0.9 | 0.9 | 0.9 | 0.9 – 1.0 | 1.0 – 1.1 |
| Factor V [IU/mL] | 0.54 – 1.45 | 0.9 | 0.9 | 0.9 | 0.6 – 0.7 | 0.9 – 1.0 |
| Factor VII [IU/mL] | 0.62 – 1.65 | 1.2 | 1.1 | 1.1 | 1.0 | 1.0 – 1.2 |
| Factor VIII [IU/mL] | 0.45 – 1.68 | 0.8 | 1.0 | 1.0 | 0.6 – 0.7 | 0.8 – 1.3 |
| Factor IX [IU/mL] | 0.45 – 1.48 | 1.4 | 1.3 | 1.5 | 0.9 – 1.0 | 1.0 – 1.3 |
| Factor X [IU/mL] | 0.68 – 1.48 | 1.0 | 1.0 | 1.1 | 0.9 – 1.0 | 1.0 – 1.1 |
| Factor XI [IU/mL] | 0.42 – 1.44 | 0.8 | 0.8 | 0.8 | 0.8 – 0.9 | 0.9 – 1.0 |
| Factor XII [IU/mL] | 0.40 – 1.52 | 1.0 | 1.0 | 1.0 | 0.9 – 1.0 | 1.0 – 1.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Factor XIII [IU/mL] | 0.65 – 1.65 | 0.9 | 0.9 | 0.9 | 1.0 – 1.1 | 0.9 – 1.0 |
| VWF:RCo [IU/mL] | 0.45 – 1.75 | 0.9 | 0.9 | 1.1 | 0.8 – 1.0 | 0.8 – 0.9 |
| ADAMTS13 [IU/mL] | 0.50 – 1.10 * | 0.9 | 0.9 | 0.9 | 1.2 – 1.5 | 0.8 – 1.2 |
| Components of the fibrinolytic and complement system | | | | | | |
| Plasminogen [IU/mL] | 0.68 – 1.44 | 0.8 | 0.9 | 0.9 | 0.8 – 1.0 | 0.8 – 0.9 |
| C3 [mg/dL] | n.d. | 94 | 96 | 101 | 100 – 111 | 93 – 108 |
| C4 [mg/dL] | n.d. | 23 | 22 | 21 | 17 – 20 | 18 – 28 |
| Protease inhibitors and cofactors | | | | | | |
| Antithrombin [IU/mL] | 0.80 – 1.25 | 1.1 | 1.0 | 1.1 | 0.8 – 0.9 | 0.9 – 1.0 |
| Heparin cofactor II [IU/mL] | 0.65 – 1.35 | 1.1 | 1.2 | 1.2 | 1.2 | 1.1 – 1.4 |
| Protein C [IU/mL] | 0.58 – 1.64 | 1.0 | 1.0 | 1.1 | 0.9 | 1.0 |
| Protein S [IU/mL] | 0.56 – 1.68 | 0.7 | 0.6 | 0.7 | 0.4 – 0.5 | 0.6 – 0.8 |
| Plasmin inhibitor [U/mL] | 0.72 – 1.32 | 0.4 | 0.5 | 0.5 | 0.4 – 0.5 | 0.4 – 0.5 |
| $\alpha_1$antitrypsin | n.d. | 1.4 | 1.2 | 1.2 | 0.9 – 1.4 | 1.0 – 1.5 |
| activity [mg/mL] | | | | | | |
| $\alpha_1$antitrypsin antigen [mg/mL] | 1.10 – 2.60 | 1.2 | 1.2 | 1.2 | 1.0 – 1.1 | 1.0 – 1.2 |
| C1-esterase inhibitor [IU/mL] | 0.60 – 1.24 | 1.2 | 1.1 | 1.2 | 0.7 – 0.8 | 1.0 – 1.5 |
| Plasma proteins (globulins and carrier proteins) | | | | | | |
| Albumin [mg/mL] | 28 – 41 | 31 | 32 | 30 | 30 – 32 | 27 – 32 |
| IgG [mg/mL] | 6.60 – 14.50 | 6.5 | 7.6 | 6.7 | 8.2 – 8.8 | 5.7 – 11.3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| IgA [mg/mL] | 0.75 – 4.20 | 1.5 | 1.5 | 1.3 | 1.5 – 1.7 | 1.3 – 1.5 |
| IgM [mg/mL] | 0.40 – 3.10 | 0.45 | 0.41 | 0.43 | 0.70 – 0.86 | 0.37 – 0.55 |
| Lipoprotein (a) [mg/dL] | 0 – 25 | 23 | 25 | 23 | 16 – 19 | 21 – 30 |
| Activation markers of the coagulation and fibrinolytic system | | | | | | |
| Factor VIIa [mIU/mL] | 25 – 170 | 79 | 68 | 83 | 55 – 72 | 54 – 76 |
| NaPTT [sec] | n.d. | 377 | 368 | 461 | 246 – 274 | 237 – 385 |
| TAT [µg/L] | 1.0 – 4.1 | < 2.0 | < 2.0 | < 2.0 | 9.5 – 11.9 | < 2.0 |
| F1+2 [nmol/L] | 0.07 – 0.23 * | 0.29 | 0.27 | 0.29 | 0.19 – 0.23 | 0.14 – 0.21 |
| D-dimer [ng/mL] | < 500 * | 101 | 115 | 106 | 62 – 129 | 106 – 147 |

**Clinical safety**

Since pharmaceutical characterisation of OctaplasLG essentially demonstrates similarity to OctaplasLG, solution for infusion (see Section III.1) the new pharmaceutical form is not expected to raise any new safety concerns. There are no new clinical safety data provided, and none are considered required.

**Risk Management Plan**

The MAH has not submitted a separate risk management plan for OctaplasLG but considers the currently approved RMP for OctaplasLG, solution for infusion also applicable for the current extension application. This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fresh frozen plasma is indicated when there is a need to provide a full range of coagulation factors to prevent or ameliorate active bleeding. OctaplasLG has been developed as a freeze-dried alternative to OctaplasLG, solution for infusion with the intention that it should have an almost identical biochemical profile as OctaplasLG. The proposed indications and posology are identical to OctaplasLG.

The development OctaplasLG is based on the manufacturing process for the licensed product and the process is identical up to the pH-adjustment prior sterile filtration.

The Quality part of the dossier is acceptably detailed. The main differences of manufacture compared to currently approved product is the lyophilisation step and the pH adjustment step prior the lyophilisation. Comprehensive biochemical characterisation has been performed and the results indicate that there are no major differences in the quality of frozen and freeze-dried product. Furthermore, the Company has decided to only use source plasma (apheresis plasma) for the manufacture of OctaplasLG. The process validation results support the use of source plasma and the lack of data from batches manufactured from recovered plasma is therefore accepted.

No new efficacy and safety studies have been provided, and none are considered required, provided that the pharmaceutical characterisation demonstrates essentially similar coagulation factor levels and activities as OctaplasLG. The new pharmaceutical form is not expected to raise any new safety concern that would require clinical study data. From a clinical perspective OctaplasLG is approvable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

**List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The decentralised procedure for octaplasLG, Powder and solvent for solution for infusion was positively finalised on 2023-02-01.

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SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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