Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

octaplasLG (plasma protein, human)

SE/W/028/pdWS/002

Marketing Authorisation Holder: Octapharma AB

Rapporteur:	Sweden
Finalisation procedure (day 120):	16 October 2020

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	octaplasLG
INN (or common name) of the active substance(s):	plasma protein, human
MAH:	Octapharma AB
Currently approved Indication(s)	• 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).
Pharmaco-therapeutic group (ATC Code):	B05AA
Pharmaceutical form(s) and strength(s):	Solution for infusion

I. EXECUTIVE SUMMARY

The MAH has submitted a final report for Study LAS-213 entitled "*An open-label multicentre, Post-Marketing Requirement study to investigate the safety, and tolerability of Octaplas^{TM} in the management of pediatric patients who require therapeutic plasma exchange"*. The study was conducted in 41 paediatric patients from 2 to 20 years of age in whom therapeutic plasma exchange (TPE) was required. The primary objective of the study was to assess the safety and tolerability. No data on efficacy is reported.

A total of 102 TPEs were given to the 41 patients. The mean volume administered per TPE was 1325 mL. The infusion rates ranged between 0.1-1.0 mL/kg/min.

There were 8 ADRs reported among 4 patients during the study. The most frequently reported ADR was mild citrate toxicity, with 2 events reported among 2 patients. There were 3 abnormal ionized calcium values reported as clinically significant by the investigators. No other safety concern was identified.

The study results provide some added reassurance regarding use in children. The issue of potential citrate toxicity warranted an update of the SmPC in section 4.2, section 4.4, and section 4.8 based on the new data. The revision mainly concerns the risk for hypocalcemia and reflects the data from the study. Corresponding information is also provided in the Package Leaflet.

II. RECOMMENDATION

The SmPC is revised in section 4.2, section 4.4, and section 4.8 based on the new paediatric data. The revision mainly concerns the risk for hypocalcemia and reflects the data from the paediatric study. Corresponding information is stated in the Package Leaflet. Although quite clinically formulated, it is suitable due to the nature of the product. The revised package leaflet is acceptable. Following agreement to the required revisions, subsequent implementation is expected in a type IB variation procedure.

SmPC section 4.2:

/…/

Paediatric population

~~The posology in children and adolescents (0-18 years) is not different to that of adults as octaplasLG is given by body weight and adjusted upon the clinical situation. Data on children and adolescents (0-18years) is presented in sections 5.1.~~ **There is limited data in children and adolescents (0-16 years) (see section 4.4,4.8and 5.1).**

Section 4.4:

/…/

Paediatric population

~~The listed warnings and precautions apply both to adults and children. Data on children and adolescents (0-18years) is presented in sections 5.1.~~**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.**

Section 4.8:

/…/

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).

A type IB variation is requested from the MAH within 30 days following the finalisation of this procedure.

III. INTRODUCTION

On 11th of March 2020, the MAH submitted a completed paediatric study for octaplasLG, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A short critical expert overview was also provided. The marketing authorisation holder proposed changes to the SmPC based on the results of the study.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Solution for infusion.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- Study LAS-213 entitled "*An open-label multicentre, Post-Marketing Requirement study to investigate the safety, and tolerability of Octaplas™ in the management of pediatric patients who require therapeutic plasma exchange"*;

2. Clinical study

Study LAS-213 entitled: "An open-label multicentre, Post-Marketing Requirement study to investigate the safety, and tolerability of OctaplasTM in the management of pediatric patients who require therapeutic plasma exchange"

- **Description**

This post-marketing requirement (PMR) study was requested by the FDA after Octaplas received marketing approval in the United States. The study was conducted in 41 paediatric and adolescent patients from 2 to 20 years of age in whom therapeutic plasma exchange was required.

The aim of the study was to obtain additional safety information on OctaplasLG in a routine clinical setting via the assessment of adverse drug reactions (ADRs), serious adverse events (SAEs), thrombotic events (TEs), and thromboembolic events (TEEs).

➢ Methods

Objective(s)

Primary Objective

The primary objective of the study was to assess the safety and tolerability of OctaplasLG in the paediatric population by monitoring SAEs, ADRs, TEs, TEEs and by measuring safety laboratory parameters.

Primary Endpoints

- SAEs, ADRs, TEs, and TEEs caused by OctaplasLG used for plasma exchange.

Secondary Endpoints

- Safety laboratory parameters (complete blood count [CBC], Chem 7 laboratory panel [Chem 7], and ionized calcium).
- Investigator's assessment of overall safety observed for each patient.

Study design

This was an open-label, multicenter, interventional, post-marketing requirement (PMR) Phase 4 study; therefore, no randomization or blinding procedures were performed.

- Study population /Sample size

Forty-one (41) patients were screened and 41 patients received at least 1 OctaplasLG infusion within the following 3 age categories:

1. Children (2 years and <12 years): a total of 15 patients
2. Children (12 years and <17 years): a total of 13 patients
3. Adolescents (≥17 years and 20 years): a total of 13 patients

For each patient, the study included up to a 14-day Screening Period, a maximum 7- day Treatment Period, and a 24-hour Follow-up Period.

Treatments

Each patient underwent a maximum 1-week (7 days) treatment period, during which their therapy included 1 or more therapeutic plasma exchange (TPE) procedures at a recommended dose of 40 to 60 mL/kg. The dose was allowed to be modified depending on the therapeutic treatment plan and the investigator's evaluation of each patient's individual clinical situation (eg, partial plasma exchanges were allowed).

Outcomes/endpoints

The primary endpoint was the rate of SAEs, ADRs, TEs, and TEEs caused by the OctaplasLG used for plasma exchange.

To facilitate the detection of any possible safety signal, SAEs, ADRs, TEs, and TEEs were characterized and analyzed by seriousness, severity, relation to study drug, and timely relationship to study drug administration.

Statistical Methods

All data collected were summarized and presented descriptively to facilitate the review of population homogeneity. Additional review in specific age sub-groups was performed, if possible. No confirmatory hypothesis testing was planned or performed. Any p-value or confidence interval presented is to be understood in the exploratory sense.

The rates of SAEs, ADRs, TEs, and TEEs were presented, together with the associated 95% confidence intervals, again per age group and in total.

Vital sign measurements (absolute values and change from Pre-TPE) were summarized by descriptive statistics, by age group and overall.

The following were also summarized descriptively, by age group, and overall: patient disposition; reasons for withdrawal; major protocol deviations; analysis populations; demographics; past and concomitant diseases; previous, maintained, and concomitant medications; physical examination; and exposure to study drug.

All safety laboratory data (CBC, Chem 7, and ionized calcium) and the investigator's assessment of overall safety were presented descriptively per TPE.

➢ Results

Recruitment/ Number analysed

In this study, 23 female patients and 18 male patients were included.

Baseline data

The youngest patients enrolled in the study was 2 years and the oldest was 20 years old. There was a high proportion of female subjects in the <12 years group. The number of patients per age group included in each analysis set are provided in the table below (Table 1).

Table 1: Number of Patients per Analysis Set

	Age Group 1 (2 – <12) N=15 N	Age Group 2 (12 – <17) N=13 N	Age Group 3 (≥17) N=13 N	All Patients N=41 N
Safety Analysis Population (SAF)	15	13	13	41
Full Analysis Set (FAS)	15	13	13	41
Per Protocol Population (PP)	15	12	13	40

Source: Table 14.1.4 N=number of patients.

Exposure

A total of 102 TPEs were given to the 41 patients. The mean volume administered per TPE was 1324.9 mL (Table 19). The infusion rates ranged from between 0.1 mL/kg/min and 1.0 mL/kg/min.

Table 19: Exposure to Study Drug – Per TPE (Safety Analysis Population, N=41)

	Age Group 1 (2 – <12) N=37	Age Group 2 (12 – <17) N=32	Age Group 3 (≥17) N=33	All Patients N=102
Volume of study drug administered [mL]				
n	37	32	33	102
Mean (SD)	709.8 (533.36)	1965.5 (600.08)	1393.3 (1012.93)	1324.9 (898.40)
Median	400.0	1985.5	813.0	1200.0
Range	113 – 1800	596 – 3320	500 – 4000	113 – 4000
Actual dose [mL/kg]				
n	37	32	33	102
Mean (SD)	27.3 (20.53)	39.3 (14.19)	19.6 (14.80)	28.6 (18.57)
Median	13.8	40.6	11.9	28.7
Range	4 – 72	10 – 64	6 – 59	4 – 72
Infusion rate [mL/kg/min]				
n	37	32	33	102
Mean (SD)	0.42 (0.156)	0.40 (0.104)	0.30 (0.074)	0.38 (0.128)
Median	0.42	0.38	0.29	0.35
Range	0.2 – 1.0	0.3 – 0.6	0.1 – 0.4	0.1 – 1.0

Efficacy results

Efficacy was not measured in the study due to the small sample size with different age groups. All patients received at least one administration of study medication and were included in the SAF and the FAS.

Safety results

No TEs or TEEs were reported by the investigators nor were identified by the IDMC during their quarterly review of the data.

There were 8 ADRs reported among 4 patients during the study. The most frequently reported ADR was mild citrate toxicity, with 2 events reported among 2 patients in Age Group 2 (12 to <17 years of age). Other ADRs reported in 1 patient each included headache, inflammatory marker increased, myalgia, nausea, pyrexia, and urticaria. Most ADRs (7/8, 87.5%) were mild and were resolved by the end of the study. Most ADRs (7/8, 87.5%) were reported in Age Group 2, 1 ADR of inflammatory marker increased was reported in Age Group 3 (17 to 20 years of age); no ADRs were reported in Age Group 1 (2 to <12 years of age).

All 8 ADRs were reported in the System Organ Class of Renal and Urinary disorders. No ADRs were reported among patients who received doses lower than 40 to 60 mL/kg dose and at higher infusion rates than recommended in the protocol and in the approved product labelling; these patients were considered to have received a partial TPE.

One patient had an unrelated serious adverse event (SAE) with a fatal outcome; this event was multiple organ failure secondary to sepsis in a 5-year-old female patient with high-risk B-cell ALL leukemia (underlying disease category of infections and infestations).

There were transient abnormal clinically significant (CS) creatinine, blood urea nitrogen (BUN), white blood cells (WBC), potassium, and glucose values reported by the investigators during the study. None of these were related to study drug and were not unexpected in this patient population.

Citrate toxicity

Citrate toxicity is a potential risk, especially when large volumes are used during a short period of time, such as for therapeutic plasma exchange.

There were a total of 28 events of ionized calcium below the normal range in 16 subjects during the study.

There were 3 cases before the first octaplas infusion, independent of citrate.

There were 11 events of ionized calcium below the normal range during a TPE and a drop in ionized calcium from the pre-TPE value to the during-TPE value.

Ten events occurred at a follow-up timepoint. Additionally, there are 4 events that occurred before the second, third or fourth TPE.

Approximately 40% of patients had a clinically relevant reduction of their pre-treatment ionized calcium level, defined as a reduction of ≥0.15 mmol/L. Most occurred during the TPE procedure.

In the TPE procedures related to hypocalcaemia events there was a trend for higher total actual doses (mL/kg) of the study drug. No such association was apparent when looking at the infusion rate of OctaplasLG.

Every subject but one received calcium supplementation in some form during the study. The majority of the calcium concomitant medications were given for an indication of "prophylaxis" or "standard of care" or "TPE". Most TPE protocols involve supplemental calcium in an effort to prevent citrate toxicity. Other specific indications are noted below.

Calcium gluconate was given to 32 of 41 subjects. Two subjects had "hypocalcemia" listed as the indication for the medication. Calcium chloride was given to 10 subjects. Two subjects had indications other than prophylaxis. Calcium carbonate was given to 8 subjects. Two subjects with indications other than prophylaxis.

It is well known that hypocalcemia occurs during plasma exchange with FFP as well as with octaplasLG because citrate is used as anticoagulant in both products. In order to minimize citrate reactions it is very often local policy to administer calcium as concomitant medication.

According to spontaneous reported events of hypocalcemia pharmacovigilance documentation did not reveal any difference in incidence between adults and pediatrics.

In a literature search hypocalcemia (a drop of ionised calcium below normal level) as such was not found to be reported as adverse drug reaction during plasma exchange. Just citrate reactions like lip tingling, pruritus, nausea/lightheadedness, chest and leg twitching. Vendramin et al. reported that a total of 5.40% of PEX procedures resulted in a documented citrate reaction (n=53, 17 female and 6 male, age 15-89) while using octaplasLG. McGuckin et al. saw within a cohort of 155 patient episodes that 15 (9.6%) had documented citrate reactions, affecting 12 females and three males (age 13-87). Compared with the literature the 5 % (2/41) citrate reactions found in the pediatric study are in line with studies in adults.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The Post-Marketing Requirement Study LAS-213 entitled *An open-label multicentre, Post-Marketing Requirement study to investigate the safety, and tolerability of Octaplas^{TM} in the management of pediatric patients who require therapeutic plasma exchange* provides relevant information regarding use in the paediatric population but conclusions are limited by the low number of patients studied and lack of control exposure. The study was conducted in 41 paediatric patients from 2 to 20 years of age in whom therapeutic plasma exchange was required. The aim of the study was to obtain additional safety information on OctaplasLG in a routine clinical setting via the assessment of ADRs, SAEs, thrombotic events (TEs), and thromboembolic events (TEEs). Efficacy was not assessed in the study. The study results provide some reassurance regarding use in children.

There were 8 ADRs reported among 4 patients during the study. Two events of mild citrate toxicity were reported among 2 patients in the age group 12 to <17 years of age. There were 3 abnormal ionized calcium values reported, judged to be clinically significant by the investigator. Other ADRs were single occurrences and no new safety concern was identified, acknowledging the small sample size and consequent limited ability to detect anything other than common events.

The potential for citrate toxicity is expected and in line with the safety profile of the product.

The study provides relevant information to further characterise the risk for citrate toxicity. A revision of the SmPC to reflect this new information has been agreed.

➢ Recommendation

The MAHs has provided a revised proposal to update the product information. The SmPC is revised in section 4.2, section 4.4, and section 4.8 based on the new paediatric data. The revision mainly concerns the risk for hypocalcemia and adequately reflects the data from the paediatric study. Corresponding information is stated in the Package Leaflet. Although quite clinically formulated, it is suitable due to the nature of the product. The revised package leaflet is acceptable. Following agreement to the required revisions, subsequent implementation is expected in a type IB variation procedure.

Section 4.2, 4.4, and 4.8 of the SmPC and corresponding sections in the PIL have been revised.

SmPC section 4.2:

/…/

Paediatric population

~~The posology in children and adolescents (0-18 years) is not different to that of adults as octaplasLG is given by body weight and adjusted upon the clinical situation. Data on children and adolescents (0-18years) is presented in sections 5.1.~~ **There is limited data in children and adolescents (0-16 years) (see section 4.4, 4.8 and 5.1).**

PL section 3:

/…/

~~**Use in children and adolescents**~~

~~As octaplasLG is given by body weight and adjusted upon the clinical situation the use in children and adolescents (0-18 years) is not different to that of adults.~~

SmPC section 4.4:

/…/

Paediatric population

~~The listed warnings and precautions apply both to adults and children. Data on children and adolescents (0-18years) is presented in sections 5.1.~~**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.**

PL section 2:

/…/

Children

~~The listed warnings and precautions apply both to adults and children.~~ **Some cases of low calcium level, possibly caused by citrate binding, have been observed during therapeutic plasma exchange in children. Monitoring of calcium is recommended during such use of octaplasLG.**

SmPC section 4.8:

/…/

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).

PL section 2:

/…/

Children

In the course of plasma exchange procedures low calcium level may be observed in children especially in patients with liver function disorders or in case of high infusion rates. Monitoring of calcium is recommended during such use of octaplasLG.

A type IB variation is requested from the MAH within 30 days following the finalisation of this procedure.

References

1. McGuckin S, Westwood J-P, Webster H, et al. Characterization of the complications associated with plasma exchange for thrombotic thrombocytopaenic purpura and related thrombotic microangiopathic anaemias: A single institution experience. Vox Sang 2014;106:161–166.
2. Vendramin C, McGuckin S, Alwan F, et al. A single-center prospective study on the safety of plasma exchange procedures using a double-viral-inactivated and prion-reduced solvent/detergent fresh-frozen plasma as the replacement fluid in the treatment of thrombotic microangiopathy. Transfusion 2017;57:131–136.