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Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Product: BALFAXAR (Prothrombin Complex Concentrate (Human))

Sponsor: Octapharma USA Inc.

**Application
Type /Number:** BLA 125776/0

Proposed indication Urgent reversal of acquired coagulation factor deficiency
induced by Vitamin K antagonist (VKA, e.g., warfarin)
therapy in adult patients with (b) (4) need
for an urgent surgery/invasive procedure.

Submission Date: July 28, 2022

PDUFA Action Due Date: July 28, 2023

1. INTRODUCTION

1.1 OBJECTIVE

The purpose of this review is to assess the adequacy of the Sponsor's pharmacovigilance plan (PVP) and to identify potential safety issues that may need to be addressed through additional postmarketing active surveillance studies, or Risk Evaluation and Mitigation Strategy (REMS), should this product be approved.

1.2 PRODUCT DESCRIPTION

BALFAXAR is a human plasma-derived, purified, virus inactivated and nanofiltered, non-activated prothrombin complex concentrate (PCC) containing the coagulation factors II, VII, IX, and X and antithrombotic Proteins C and S. BALFAXAR is supplied as a lyophilized powder for reconstitution for intravenous use. BALFAXAR is sterile, endotoxin-free, and does not contain preservatives. No albumin is added as a stabilizer. The diluent for reconstitution of the lyophilized powder is sterile water for injection.

The nominal composition of BALFAXAR is displayed in Table 1.

Table 1. Nominal composition of BALFAXAR

Component	Potency Range for 500 IU vial	Potency Range for 1000 IU vial
Human Coagulation Factor II	(b) (4)	(b) (4)
Human Coagulation Factor VII	(b) (4)	(b) (4)
Human Coagulation Factor IX	(b) (4)	(b) (4)
Human Coagulation Factor X	(b) (4)	(b) (4)
Protein C	(b) (4)	(b) (4)
Protein S	(b) (4)	(b) (4)
Heparin	(b) (4)	(b) (4)
Sodium Citrate	(b) (4)	(b) (4)

All human plasma used in the manufacture of BALFAXAR is obtained from US donors, collected in FDA-approved blood and plasma establishments, and tested by FDA-licensed serological tests for viral markers (Hepatitis B surface antigen (HBsAg), antibodies to HIV-1/2 and HCV). The plasma is tested with Nucleic Acid Testing (NAT) for HCV, HIV-1, HAV, and HBV, and found to be non-reactive (negative), and the plasma is also tested by NAT for human parvovirus B19 (B19V) in order to exclude donations with high titers. The limit for the titer of B19V DNA in the manufacturing pool is set not to exceed 104 IU/mL. Only plasma that passed virus screening is used for production.

The BALFAXAR manufacturing process has the capability to inactivate/remove viruses by a solvent/detergent (S/D) virus inactivation step and a virus removal nanofiltration step.

The preparation complies with the monograph on Human Prothrombin Complex (freeze-dried) of the (b) (4)

1.3 PROPOSED INDICATION, DOSAGE FORM AND STRENGTH

BALFAXAR, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.

BALFAXAR is a sterile, white to ice-blue lyophilized powder for reconstitution for intravenous use. It is provided in a single-dose vial with a nominal strength of 500 Factor IX units in 20 mL reconstitution volume and 1000 Factor IX units in 40 mL reconstitution volume per vial. BALFAXAR contains the coagulation factors II, VII, IX, and X and antithrombotic Proteins C and S.

1.4 PERTINENT REGULATORY HISTORY

BALFAXAR is currently approved in 86 countries worldwide under the foreign brand name of *Octaplex* and was first approved in Germany on March 14, 2003. (b) (4)

This was agreed to by Octapharma and the sponsor conducted the non-inferiority trial Study LEX-209 in patients needing urgent surgery with significant bleeding risk. LEX-209 is the pivotal study for this BLA (125776).

At the pre-BLA, Type B meeting held on November 17, 2021, Octapharma aimed to reach agreement with the FDA on the format and content of a new BLA submission supported by interim clinical data, for reversal of anticoagulation due to VKA in patients needing urgent surgery associated with significant bleeding risk.

This memo will use the name *Octaplex* to refer to BALFAXAR, the name of the product in BLA 125776/0, when referring to the product safety and efficacy data from clinical trials and to postmarketing safety data.

2. MATERIALS REVIEWED

The materials reviewed in support of the assessment are listed below:

- FDA's written responses to the pre-BLA, Type B meeting from November 17, 2021 (under BB-IND #013323)
- Reports of completed clinical studies LEX-201, LEX-202, LEX-203, LEX-204, LEX-205, LEX-206 and LEX-209 (BLA 125776/0, received July 28, 2022)
- Overview Safety Summary (OSS) for *Octaplex* (BLA 125776/0, received July 28, 2022)
- Summary of Clinical Safety of *Octaplex* (BLA 125776/0, received July 28, 2022)
- Clinical Overview of *Octaplex* (BLA 125776/0, received July 28, 2022)
- Octapharma Safety Summary No.02, dated June 20, 2022 (BLA 125776/0, received July 28, 2022)
- Risk Management Plan No. 06.2, dated July 21, 2022, which includes the US Specific Addendum No. 03 to EU-RMP, dated July 25, 2022 (BLA 125776/0, received July 28,

2022)

- Proposed labeling text (BLA 125776/0, received July 28, 2022)
- *Octaplex* PVP review memo, dated (b) (4) (under (b) (4))
- Response to FDA's Jan 23, 2023 IR, received February 3, 2023 as Amendment #013 to STN 125776/0.
- Risk Management Plan No. 06.2a, dated February 2, 2023 which includes the US Specific Addendum No. 04 to EU-RMP, dated February 2, 2023 (BLA 125776/0, received February 3, 2023).
- Response, to FDA's March 17, 2023 IR (received March 27, 2023 as Amendment #030 to STN 125776/0).
- Response to FDA's May 18, 2023 IR (received May 24, 2023 as Amendment #036 to STN 125776/0).
- Response to FDA's June 12, 2023 IR (received June 15, 2023 under STN 125776/0, Amendment #042)

3. CLINICAL TRIAL EXPERIENCE

3.1 OVERVIEW

The clinical data included in this application are intended to support the following indications and labeling:

- urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with (b) (4) need for an urgent surgery/invasive procedure.

Octapharma submitted in this BLA seven completed clinical studies: LEX-201, LEX-202, LEX-203, LEX-204, LEX-205, LEX-206 and LEX-209. Of note, in FDA's written responses to the pre-BLA, Type B meeting from November 17, 2021 (under BB-IND #013323), the FDA agreed that integration of safety and efficacy data from clinical studies evaluating *Octaplex* would not be valid, due to substantial differences between study designs (e.g., populations, endpoints, and drug product dosages). Therefore, the FDA agreed with Octapharma's proposed submission of individual study results. Assessments of relatedness reflect investigator's opinion unless noted otherwise. Please refer to Appendix 1 for a tabular listing of completed clinical studies with *Octaplex*.

3.2 SAFETY ANALYSIS OF STUDY LEX-209

LEX-209 is the pivotal study for this BLA and is a Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of *Octaplex*, a four-factor prothrombin complex concentrate (4F-PCC), compared to the 4F-PCC Beriplex® P/N (US proprietary name Kcentra), for the reversal of VKA induced anticoagulation in patients needing urgent surgery with significant bleeding risk. The primary endpoint was haemostatic efficacy rating at the end of surgery. Safety endpoints included: AEs, thromboembolic events (TEEs), mortality, vital signs, laboratory safety and viral safety. The duration of the entire study for each patient was approximately 45 days. Refer to Appendix 1 for additional details on study design and outcomes.

The dose tested in LEX-209 depended on the body weight (BW) and baseline international normalized ratio (INR) (INR0) of the patient and was calculated by the

responsible treating investigator as follows:

Baseline INR (rounded to the first decimal place)	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW) (BW rounded to the nearest whole kilogram)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

The product was administered by intravenous (IV) infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).

The study was conducted in two stages, with one unblinded interim analysis after enrollment of 50% of the planned sample size, to allow for an early stopping of the study for demonstrated noninferiority or to allow for an early stopping due to futility to achieve this. The safety population included 105 subjects in the *Octaplex* group and 103 subjects in the Kcentra group.

3.2.1. All AEs

A total of 208 patients were randomized to study treatment and included in the safety analysis (SAF) population. Of the 105 patients in the *Octaplex* group, 86 patients (81.9%) experienced a total of 177 TEAEs. Of the 103 patients in the Beriplex® P/N (Kcentra) group, 80 patients (77.7%) experienced a total of 212 TEAEs. (Table 2)

There were 5 patients (4.8%) with TEAEs with a fatal outcome in the *Octaplex* group versus 1 (1.0%) in the Beriplex® P/N (Kcentra) group. The incidence of TEAEs leading to study discontinuation, drug-related TEAEs, and drug related SAEs was similar in the two treatment groups (Table 3).

Table 2. Overall Summary of Adverse Events (Safety Analysis Set)

TEAE Category	<i>Octaplex</i> N=105		Kcentra N=103	
	Patients n (%)	Events e (%)	Patients n (%)	Events e (%)
Any TEAE	86 (81.9)	177 (100)	80 (77.7)	212 (100)
Any Serious TEAE	13 (12.4)	21 (11.9)	6 (5.8)	9 (4.2)
TEAE with Fatal Outcome	5 (4.8)	5 (2.8)	1 (1.0)	1 (0.5)
Drug Related Serious TEAE	1 (1.0)	1 (0.6)	0	0
Any TEAE Leading to Study Discontinuation	1 (1.0)	1 (0.6)	1 (1.0)	1 (0.5)
Drug Related TEAE	1 (1.0)	2 (1.1)	1 (1.0)	1 (0.5)

The most commonly reported TEAEs by SOC (>10% in either group) were injury, poisoning and procedural complications (in 69.5% of patients in the *Octaplex* group and 65.0% in the Beriplex® P/N [Kcentra] group), general disorders and administration site

conditions (in 20.0% and 25.2%, respectively), gastrointestinal disorders (in 10.5% and 18.4%, respectively), and investigations (in 0% and 11.7%, respectively) (Table 3). The most commonly reported TEAEs by PT (>5% in either group) were procedural pain (in 47.6% of patients in the *Octaplex* group and 48.5% in the Beriplex® P/N [Kcentra] group), postoperative wound complication (in 14.3% and 14.6%, respectively), asthenia (in 12.4% and 17.5%, respectively), and anaemia (in 5.7% and 5.8%, respectively) (Table 3).

Table 3. Display of Treatment-Emergent Adverse Events (Frequency >2.0% of Patients in the *Octaplex* Group) by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	<i>Octaplex</i> N=105 n (%)	Kcentra N=103 n (%)
Any TEAE	86 (81.9)	80 (77.7)
Blood And Lymphatic System Disorders	7 (6.7)	7 (6.8)
Anaemia	6 (5.7)	6 (5.8)
Cardiac Disorders	5 (4.8)	7 (6.8)
Gastrointestinal Disorders	11 (10.5)	19 (18.4)
Abdominal Pain	3 (2.9)	5 (4.9)
General Disorders And Administration Site Conditions	21 (20.0)	26 (25.2)
Asthenia	13 (12.4)	18 (17.5)
Catheter Site Related Reaction	4 (3.8)	2 (1.9)
Hyperthermia	3 (2.9)	2 (1.9)
Injury, Poisoning And Procedural Complications	73 (69.5)	67 (65.0)
Procedural Pain	50 (47.6)	50 (48.5)
Postoperative Wound Complication	15 (14.3)	15 (14.6)
Procedural Vomiting	4 (3.8)	0
Metabolism And Nutrition Disorders	4 (3.8)	7 (6.8)
Musculoskeletal And Connective Tissue Disorders	5 (4.8)	1 (1.0)
Nervous System Disorders	6 (5.7)	1 (1.0)
Renal And Urinary Disorders	6 (5.7)	5 (4.9)
Dysuria	5 (4.8)	2 (1.9)

MedDRA=Medical Dictionary for Regulatory Activities; N,n=number of patients; TEAE=treatment-emergent adverse event.

One patient (1.0%) in the *Octaplex* group had 2 treatment-related events (angina unstable and chest pain), and 1 patient (1.0%) in the Beriplex® P/N (Kcentra) group had a treatment-related event of blood lactate dehydrogenase increased.

TEAEs of mild/moderate severity developed in 77 (73%) and 72 (70%) subjects in the *Octaplex* group and the Beriplex® P/N [Kcentra] group, respectively. Severe TEAEs developed in 9 (8.6%) and 8 (7.8%) of subjects in the *Octaplex* group and the Beriplex® P/N [Kcentra] group, respectively.

Reviewer comment

The number of patients with TEAEs with a fatal outcome was higher in the *Octaplex* group than in the Beriplex® P/N (Kcentra) group (5 (4.8%) versus 1 (1.0%), respectively).

Overall, the proportion of patients with TEAEs was similar in the two treatment groups.

Generally, the incidence of TEAEs by PT was similar across the two treatment groups.

TEAEs leading to study discontinuation and drug-related TEAEs, were low and similar in both treatment groups. The majority of TEAEs were moderate or mild in intensity in both groups.

3.2.2 Deaths

Five patients (4.8%) in the *Octaplex* group had SAEs with a fatal outcome including an 89-year-old white female who died of a pulmonary embolism 37 days after receiving investigational product (IP), a 90-year-old white male who died of an unspecified cause 35 days after receiving IP for urgent evacuation of chronic subdural hematoma, a 73-year-old white female who died of chronic cardiac failure 24 days after receiving IP, a 90-year-old white female who died of ischemic heart disease 30 days after receiving IP, and a 74-year-old white male who died of multiple organ dysfunction syndrome 47 days after receiving IP and after completing the last study visit. All deaths in the *Octaplex* group occurred more than 22 days post-surgery.

One (1.0%) in the Beriplex® P/N (Kcentra) group had an SAE with a fatal outcome. The subject was a 93-year-old white female who died of acute cardiac failure 10 days after receiving IP.

The Risk Ratio of *Octaplex* vs Kcentra (95% CI) was 4.90 (0.58, 41.26). All SAEs with a fatal outcome were considered not related to IP by the investigator.

Reviewer comment

A numerically higher proportion of patients experienced SAEs with a fatal outcome in the *Octaplex* group (this numerical imbalance was not statistically significant).

3.2.3 Serious Adverse Events

Thirteen patients (12.4%) in the *Octaplex* group and 6 patients (5.8%) in the Beriplex® P/N (Kcentra) group had SAEs. In the *Octaplex* group, SAEs were most commonly reported (>2%) in the SOC of injury, poisoning and procedural complications (4 subjects, 3.8%), cardiac disorders (3 subjects, 2.9%) and gastrointestinal disorders (3 subjects, 2.9%). In the Beriplex® P/N (Kcentra) group there were no SOC with an incidence >2%.

There were 21 serious TEAEs in the *Octaplex* group including one event each of pulmonary oedema, soft tissue hemorrhage, cerebral infarction, pulmonary embolism, subdural hemorrhage, death, angina unstable, joint dislocation, gastritis erosive, cardiac failure chronic, myocardial ischemia, anastomotic hemorrhage, failure to anastomose, multiple organ dysfunction syndrome, orchitis, proctitis, and mesenteric hematoma and, 2 events each of shock and acute respiratory failure.

There were 9 serious TEAEs reported in the Beriplex® P/N (Kcentra) group: ileus, gastritis hemorrhagic, shock hemorrhagic, hemorrhagic anemia, anemia, pneumonia, cardiac failure acute, ovarian cancer stage IV, and postoperative wound complication.

One SAE was determined to be related to IP by the investigator. One subject in the *Octaplex* group (a 63-year-old white male) developed an SAE of unstable angina of moderate severity with onset on Day 5 which resolved the same day. Medical history included arterial hypertension III (ESCESH), coronary artery disease, angioplasty and stenting (2018), permanent atrial fibrillation, heart failure, and laryngeal cancer. The patient was receiving VKA therapy as he was considered a high risk of thrombosis (permanent atrial fibrillation) and was enrolled into the study for urgent reversal of VKA therapy in preparation for major orthopedic surgery. The event was considered possibly related to study drug. There was no transfusion done during the intraoperative period.

Reviewer comment

A higher proportion of patients experienced SAEs in the *Octaplex* group versus the Beriplex group. In the *Octaplex* group, one subject with CVL risk factors developed a related SAE and TEE of unstable angina.

3.2.4 Thromboembolic events

Four TEEs were reported in 3 patients (2.9%) in the *Octaplex* group; no TEEs were reported in the Beriplex® P/N (Kcentra) group:

- A 63-year-old white male developed a drug-related SAE of unstable angina on Day 5 (Please refer to section 3.2.3. Serious Adverse Events).
- An 89-year-old white female experienced 2 TEEs: the first was cerebral infarction 12 days after receiving IP and the second TEE was pulmonary embolism 37 days after receiving IP, which had a fatal outcome. Both events were considered not related to IP by the investigator. Relevant medical history included hypertension, congestive heart failure, ischemic heart disease, permanent atrial fibrillation, non-rheumatic mitral valve stenosis and insufficiency with secondary pulmonary hypertension, acute vascular disorders of intestine (mesenteric artery thrombosis), and diabetes mellitus. The patient was enrolled into the study for urgent laparotomy for an intestinal obstruction (mesenteric artery thrombosis) requiring reversal of VKA therapy that the patient was receiving for permanent atrial fibrillation. The patient received multiple post-operative blood transfusions.
- A 90-year-old white female had a TEE of myocardial ischemia 30 days after receiving IP which had a fatal outcome. The event was considered not related to IP by the investigator. Relevant medical history included rheumatoid arthritis, ischemic heart disease, arterial hypertension, chronic cardiac failure, atrial fibrillation, and

intertrochanteric fracture of the right femur. Patient was receiving VKA therapy considering presence of prothrombotic condition (paroxysmal form of atrial fibrillation) and was enrolled into the study for reversal of VKA therapy in preparation for urgent surgery. The patient received 1 intraoperative blood transfusion.

Reviewer comment

TEEs were only reported among patients in the *Octaplex* group and none in comparator (Kcentra) group. Two of the three subjects with TEEs had fatal outcomes. Two of the TEEs were reported in the period from 4 to 21 days post-surgery, and the other 2 TEEs were reported as having occurred between 22 to 45 days post-surgery. Based on these patients' medical histories, comorbidities, and concomitant therapies (e.g., intraoperative and/or postoperative blood transfusion), multiple thrombotic risk factors were present. One of the 4 TEEs was considered by the investigator to be possibly related to study drug. Arterial and venous thromboembolic complications are labeled events in the proposed BALFAXAR USPI.

3.2.5. Other Significant Adverse Events

One patient (1.0%) in the *Octaplex* group and two patients (1.9%) in the Kcentra group had negative nucleic acid values for parvovirus B-19 at baseline and a positive value post-baseline; no patients had a seroconversion based on serology testing.

Reviewer comment

When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting viruses cannot be completely eliminated. Transmission of infections by this product is a labeled event in the proposed BALFAXAR USPI.

3.3 SAFETY ANALYSIS OF STUDY LEX-205

LEX-205 is considered a key supportive study of this application. LEX-205 is a randomized, open-label, efficacy and safety study of *Octaplex* and Fresh Frozen Plasma (FFP) in patients under VKA therapy with INR >2 undergoing a minor surgery or procedure with a low bleeding risk.

Primary endpoints were correction of INR to < 1.5 15 minutes after the end of first infusion and number of intra-operative red blood cell units (RBC) transfused. Safety endpoints included: thrombogenicity, clinical tolerability (adverse events, vital signs, laboratory safety) and viral safety.

The duration of the entire study for each patient was 6 months. Refer to Appendix 1 for additional details on study design and outcomes.

Safety population (safety set) included 97 subjects in the *Octaplex* group and 103 subjects in the FFP group.

3.3.1 All AEs

There were 362 TEAEs in the *Octaplex* group and 383 TEAEs in the FFP group during the 21-day observation window. Overall, 67 (69%) patients in the *Octaplex* group and 76 (74%) in the FFP group developed AEs.

Reviewer comment

The number of TEAEs was similar in both treatment groups. The percentage of patients in the *Octaplex* group with any AE was slightly smaller compared with the FFP group. In view of the small numbers involved it is difficult to discern any systematic trend in any of the between-group differences. Refer to *Octaplex* PVP review memo ((b) (4)) under ((b) (4)) for additional information on all AEs.

3.3.2 Deaths

Deaths due to TEAEs in the entire study period were reported for 19 (20%) subjects in the *Octaplex* group and 13 (13%) subjects in the FFP group. Deaths due to TEAEs within 21 days after the end of infusion occurred in 9 (9%) subjects in the *Octaplex* group and 5 (5%) subjects in the FFP group.

Causes of death in the *Octaplex* group included one case each of: CAD, infarct, cardiovascular insufficiency, peripheral ischemia, gangrene, post procedural hemorrhage, postoperative respiratory distress, respiratory arrest, respiratory failure, brain compression, prostate cancer, failure to thrive, and unknown cause. Two patients each died of cardiac arrest, renal failure and multiorgan failure.

Causes of death in the FFP group included: right ventricular failure, myocardial infarction, cardiac failure acute, cardiogenic shock, endocarditis bacterial, respiratory failure, pneumonia, condition aggravated (subdural hematoma), sepsis, renal failure acute and renal failure chronic. For 2 subjects cause of death was unknown.

Reviewer comment

There were more deaths in the *Octaplex* group than in the FFP group overall and within 21 days after end of infusion. The overall causes of deaths showed no clear or systematic differences between the treatment groups. Refer to *Octaplex* PVP review memo ((b) (4)) under ((b) (4)) for additional information on death cases.

3.3.3 Serious Adverse Events

A total of 178 SAEs were reported in 91 patients (46%); 96 of these SAEs were reported in 47 patients (49%) in the *Octaplex* group and 82 SAEs were reported in 44 patients (43%) in the FFP group.

Related and severe SAEs in the *Octaplex* group included 4 TEEs: 2 events each of deep vein thrombosis and one case each of pulmonary embolism and thrombosis in the device. Related and severe SAEs in the FFP group included: one case each of acute respiratory distress syndrome, supraventricular tachycardia, cardiac failure, respiratory distress and cardiogenic shock.

Reviewer comment

Numbers of SAEs were slightly greater in the *Octaplex* group than in the FFP group. All related severe SAEs in the *Octaplex* group were TEEs. There were no related severe SAEs of TEE in the FFP group. Refer to *Octaplex* PVP review memo ((b) (4)) under ((b) (4)) for additional information on SAEs.

3.3.4. Thromboembolic events

There were 27 TEEs among 14 (14.4%) patients in the *Octaplex* group. These 27 TEEs represented 7.5% (or 27/362) of all TEAEs in the 21-day period and 4.4% (or 27/613) of all TEEs in the entire study period.

There were 12 TEEs among 10 (9.7%) patients in the FFP group. These 12 TEEs represented 3% (or 12/383) of all TEAEs in the 21-day period and 2 % (or 12 /562) of all TEEs in the entire study period.

Reviewer comment

The percentage of subjects with TEEs was higher in the *Octaplex* group compared with the FFP group within 21 days after end of infusion and overall. Refer to *Octaplex* PVP review memo ((b) (4)) under (b) (4)) for additional information on TEEs.

Arterial and venous thromboembolic complications are labeled events in the proposed BALFAXAR USPI in the following sections: Boxed Warning, Warnings and Precautions, Adverse Reactions (6.1 Clinical Trials Experience and 6.2 Postmarketing Experience).

3.4 UNCONTROLLED STUDIES

Uncontrolled studies include LEX-201, LEX-202 and LEX-203 and LEX-206. Refer to *Octaplex* PVP review memo ((b) (4)) under (b) (4)) for safety information from these studies.

Reviewer comment

There were reports of TEEs in uncontrolled studies, mostly considered unrelated to IP. Arterial and venous thromboembolic complications and transmission of infections are labeled events in the proposed BALFAXAR USPI.

There were also instances of related Parvovirus B19 seroconversion. It is well known that the current state-of-the-art production technique of factor concentrates is not effective in inactivating non-enveloped viruses such as Parvovirus B19.

Transmission of infections is a labeled event in the proposed BALFAXAR USPI.

4. POST LICENSURE SAFETY REVIEW

Post licensure studies include LEX 204 and OPTIPLEX (French multicenter observational study). Other non-interventional studies included the study at Ottawa General Hospital, Canada. Investigator-initiated interventional clinical trials included the INCH (ICH-VKA). Study.

Please refer to *Octaplex* PVP review memo ((b) (4)) under (b) (4)) for safety information from these studies.

4.1 OVERVIEW SAFETY SUMMARY

The Overview Safety Summary (OSS) for *Octaplex* submitted in BLA 125776 covers the period from March 14, 2003 (international birth date, IBD) to March 31, 2022. The report summarizes the safety information from *Octaplex* PSURs No. 01 to 25 and additionally covers the period from May 1, 2021 to March 31, 2022.

Since the IBD about (b) (4) IU of *Octaplex* have been sold worldwide, which correspond to approximately (b) (4) patients exposed (based on mean single dose of approximately 30 IU/kg BW and a mean patient weight of 70 kg).

The OSS provides a cumulative overview of the *Octaplex* serious ICSRs received by Octapharma from worldwide reporting sources since IBD, including findings from observational and investigator-initiated clinical trials.

There were 50 serious reports indicative of hypersensitivity or an anaphylactic reaction with 4 fatal outcomes, 66 reports indicative of TEE (2 reported in children) with 7 fatal outcomes, 2 reports of heparin-induced thrombocytopenia with one fatal outcome, and 2 reports of *Octaplex* exposure during pregnancy (patients experienced no adverse reactions).

Cumulatively, the sponsor received 18 initial ICSRs with a fatal outcome with *Octaplex* as suspect drug. A causal relationship could not be excluded in the following death cases: cardiac arrest/respiratory failure, cerebral thrombosis, pancreatitis / thrombocytopenia / thrombotic microangiopathy / c-reactive protein increased, brain stem stroke, anaphylactic shock, cardio-respiratory arrest and cardiac arrest.

There was a case of death associated with administration of *Octaplex* in error to a subject with TTP. There was also a life-threatening event of anaphylaxis plus massive pulmonary embolism in a subject originally admitted to the hospital with possible pulmonary embolism who received *Octaplex* SC in error. There were additional post-marketing reports of medication errors consisting of: administration of incorrect dose (underdose/overdose), administration of *Octaplex* when contraindicated / not indicated, administration errors connected to other products with similar name (Octaplas, Octagam, Octafix Vialebex) and errors in preparation / reconstitution and administration.

Reviewer comment:

The pattern of adverse events in the post-marketing setting is consistent with underlying medical conditions that require use of VKA and/or result from complications associated with the use of VKAs or *Octaplex*.

Arterial and venous thromboembolic complications, hypersensitivity reactions (including anaphylactic reactions) and transmission of infections are labeled events in the proposed BALFAXAR USPI. Some medication errors resulted in death or life-threatening events.

Since the IBD, no actions relating to the safety of *Octaplex* have been taken by regulatory authorities or by the marketing authorization holder.

4.2 Data mining with Empirica

Data mining was performed with Empirica Signal on August 19, 2022 (as of date August 14, 2022) to discern events disproportionally reported following the use of *Octaplex* compared to all products in the FAERS database. A disproportional reporting alert is defined as an EB05 >2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean. The search revealed 2 preferred terms (PTs) with an EB05 greater than 2 associated with *Octaplex*. The PTs with EB05 > 2 are listed in Table 4 below.

Table 4. Label Status of PTs with EB05 > 2

Product name	PT	SOC	N	EB05
OCTAPLEX	Dyspnoea	Resp	5	2.032
OCTAPLEX	Shock	Vasc	5	56.396

Reviewer Comment:

In some rare cases reports of non-FDA approved drugs appear in FAERS. This may occur when other drugs were used (identified as concomitant or suspect). The PTs of dyspnoea and shock can be explained in the context of underlying medical indications of *Octaplex* (in countries where it is approved) such as bleeding and perioperative prophylaxis of bleeding.

4.3 FDA Adverse event reporting System (FAERS)

A search was conducted of the FDA Adverse Event Reporting System (FAERS) on August 19, 2022 to evaluate adverse events after *Octaplex* infusion. The search retrieved 20 serious FAERS reports. PTs are shown in Table 5.

Table 5. PTs with *Octaplex* in FAERS (frequency $\geq 15\%$, or at least 3 events)

Preferred Terms	Total Cases	% of Cases
Dyspnoea	7	35.0%
Shock	5	25.0%
Atelectasis	4	20.0%
Blood pressure increased	4	20.0%
Body temperature increased	4	20.0%
Cardiomegaly	4	20.0%
Hypervolaemia	4	20.0%
Cerebral haemorrhage	3	15.0%
Drug ineffective	3	15.0%
Hepatic failure	3	15.0%
Urticaria	3	15.0%

Among the 20 serious FAERS reports there were 6 reports of death corresponding to 5 unique cases: 1) suicide (colchicine poisoning), 2) pulmonary edema, 3) medication error, 4) cardiopulmonary arrest with total thrombosis of right coronary artery and coronary bypass thrombosis and, 5) anaphylactic shock (secondary to Thymoglobulin treatment), versus "shock status" due to a massive pulmonary embolism.

Reviewer Comment

The interpretation of the PTs in Table 5 has limited value due to the low number of serious reports in FAERS. Most PTs involve medical conditions that are comorbidities in

subjects receiving *Octaplex* (not associated with the use of *Octaplex* per se) such as *atelectasis*, *blood pressure increased*, *body temperature increased*, *cardiomegaly* or resulting from the use of VKA (i.e., *cerebral hemorrhage*, *shock*). The PT of *urticaria* may represent a true complication of treatment with *Octaplex*. Hypersensitivity reactions, including anaphylactic reactions, are labeled events in the proposed BALFAXAR USPI.

5. PHARMACOVIGILANCE PLAN

5.1 Safety Issues

Safety issues identified by the applicant and the applicant's proposed risk mitigation strategies are described in the EU Risk Management Plan for *Octaplex*, Version No. 06.2, dated July 21, 2022 and in the US Specific Addendum No. 03 to EU-RMP, dated July 25, 2022 submitted under 125776/0. The Addendum includes a risk minimization plan detailing routine risk minimization measures proposed for BALFAXAR according to the proposed US prescribing information and the pharmacovigilance plan. In response to FDA's Jan 23, 2023 IR (received February 3, 2023 under STN 125776/0, Amendment #013) the sponsor revised the EU-RMP to Version No. 06.2a, which includes medication errors and transmission of an infectious agent as important identified risks. Additionally, the US Addendum to the EU-RMP was revised to version No. 04, which describes the planned measures for both risks.

In response to FDA's May 18, 2023 IR (received May 24, 2023 under STN 125776/0, sequence #0037) the sponsor revised the US Addendum to the EU-RMP to version No. 05 as a result of the following updates:

- Section 2.3 *Routine Pharmacovigilance Activities* for the safety concern of TEEs now includes the following enhanced pharmacovigilance measures for a period of 3 years following approval of BALFAXAR:
 - Submission of expedited (15-day) reports for all TEEs regardless of seriousness or expectedness of the event
 - Provide aggregate assessment (based on interval and cumulative data) of TEEs in periodic safety reports.
- Section 2.4 *Additional Pharmacovigilance Activities*. This section was added, as requested, to propose conducting LEX-212 as a postmarketing requirement (PMR) should BALFAXAR be approved. LEX-212 is an observational study of safety in patients treated with BALFAXAR for reversal of vitamin k antagonist induced anticoagulation in patients needing urgent surgery or an invasive procedure. This new section also includes a summary of the PMR study (Refer to Appendix 2).

In response to FDA's June 12, 2023 IR (received June 15, 2023 under STN 125776/0, Amendment #42) the sponsor agreed to adding *Proportion of patients with TEEs within 45 days following VKA reversal treatment with BALFAXAR compared to Kcentra* the primary study endpoint and *Proportion of patients who die from any reason within 45 days following VKA reversal treatment with BALFAXAR compared to Kcentra* the secondary study endpoint in the final protocol.

The sponsor also confirmed that the study is planned to enroll at least 3575 patients randomized 1:1 to BALFAXAR or active comparator and the following study milestones:

Estimated protocol submission date: 12/31/2023
 Estimated study initiation date: 06/30/2024
 Estimated study completion date: 12/31/2031
 Estimated final report submission date: 06/30/2032

Based on a 45-day incidence rate of TEEs of 3% and one-sided level of alpha = 0.025, a sample size of 3575 will provide a 90% study power to test the primary endpoint.

Routine Pharmacovigilance Practices and Risk Minimization Measures for BALFAXAR are summarized in Table 6 below (adapted from Parts II to VI of the EU Risk Management Plan for *Octaplex*, Version No. 06.2a, and Section 2.3 *Routine Pharmacovigilance Activities* and 2.4 *Additional Pharmacovigilance Activities* of the US Specific Addendum No.05 to EU-RMP).

Table 6. Sponsor-Proposed Pharmacovigilance Plan for BALFAXAR

Safety Concern	Planned action
Important Identified Risks	
Hypersensitivity reactions, including anaphylactic reactions	<ul style="list-style-type: none"> • Routine pharmacovigilance (adverse reactions reporting and signal detection) • Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: <ul style="list-style-type: none"> Section 4 Contraindications Section 5.1 Hypersensitivity reactions Section 6.2 Postmarketing Experience Section 17 Patient counselling information

Thromboembolic events	<ul style="list-style-type: none"> Enhanced pharmacovigilance for three years following approval: <ul style="list-style-type: none"> ✓ Reporting of all post-marketing TEEs regardless of seriousness or expectedness of the event as expedited (15-day) reports ✓ Provision of aggregate assessment (based on interval and cumulative data) of TEEs in periodic safety reports Post-marketing requirement (PMR) of prospective observational study of patients treated with BALFAXAR or Kcentra for reversal of vitamin K antagonist anticoagulation in the setting of urgent surgery or an invasive procedure with a 45-day follow up Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: BOXED WARNING Section 5.2 Thromboembolic Risk/ Complications Section 6.1 Clinical Trials Experience Section 6.2 Postmarketing Experience Section 13.2 Animal Toxicology and/or Pharmacology Section 17 Patient counseling information Signal detection
Heparin induced thrombocytopenia	<ul style="list-style-type: none"> Routine pharmacovigilance (adverse reactions reporting and signal detection) Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: Section 4 Contraindications
Transmission of an infectious agent	<ul style="list-style-type: none"> Routine pharmacovigilance (adverse reactions reporting and signal detection) Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: Section 5.3 Transmission of infectious agents Section 11 Description Section 17 Patient counselling information

Medication errors	<ul style="list-style-type: none"> • Routine pharmacovigilance (adverse reactions reporting and signal detection) • The proposed brand name 'BALFAXAR' reduces the risk of administering other products in error. • Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: Section 2.1 Dosage Section 2.2 Preparation and reconstitution Section 2.3 Administration Section 4 Contraindications Section 16 How supplied/storage and handling
Important Potential Risks	
Development of neutralizing antibodies / inhibitor development	<ul style="list-style-type: none"> • Routine pharmacovigilance (adverse reactions reporting and signal detection) • Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: Section 8.6 Congenital Factor Deficiencies
Missing information	
Safety in paediatric population	<ul style="list-style-type: none"> • Routine pharmacovigilance (adverse reactions reporting and signal detection) • Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: Section 8.4 Pediatric Use
Safety in pregnant and breastfeeding women	<ul style="list-style-type: none"> • Routine pharmacovigilance (adverse reactions reporting and signal detection) • Routine risk minimization measures: <ul style="list-style-type: none"> ✓ Proposed text in USPI is included in the following sections: Section 5.3 Transmissible Infectious Agents Section 8.1 Pregnancy Section 8.2 Lactation

5.1.1 Routine Pharmacovigilance Practices

The US Specific Addendum No. 05 to EU-RMP, dated May 24, 2023, submitted under 125776/0 includes: 1) Procedures for expedited reporting of SAEs and unexpected SAEs as well as for the handling of periodic and systematic literature searches with regards to

Adverse Drug Reactions (ADRs), 2) Processes of signal detection and trend analyses performed for all Octapharma-branded products, and 3) Standards and time periods for aggregate reporting.

The processes described in the Standard Operating Procedures (SOPs) and Working Instructions (WOIs) included in the US Specific Addendum No. 05 to EU-RMP outline procedures to ensure:

- The collection and collation of information about all reported ADRs in an accessible manner.
- The preparation of reports (e.g., expedited ADR reports and PADERS) for regulatory authorities in an accurate and timely manner.
- The continuous monitoring of the safety profile of products including signal detection, issue evaluation, updating of labeling and contact with regulatory authorities.
- Standards and time periods for aggregate reporting.
- Other requirements as defined by local regulations.

Reviewer comment:

Routine and enhanced pharmacovigilance and AE reporting are in accordance with 21 CFR 600.80.

5.1.2 Pharmacovigilance Methods

The following main activities are performed at the Corporate Octapharma Drug Safety Department and Medical Writing Department (Vienna, Austria),

- Central collection and processing of adverse event reports
- Preparation of expedited reports and regulatory notification either via local affiliates or directly with regulatory authorities
- Preparation of periodic reports (Periodic Adverse Experience Reports)
- Signal detection and trend analysis
- Case report, and batch and lot number, reviews
- Preparation of risk management plans
- Liaising with regulatory authorities on safety-related enquiries.

Local Drug Safety Officers are responsible for local and regional processing of safety reports, including recording and forwarding appropriate data to the Corporate Drug Safety Unit. Local Drug Safety Officers are also responsible for following up with the reporters of ADRs and relaying the appropriate report forms from the Corporate Drug Safety Unit, as applicable, to the respective national regulatory authorities. Case safety reports are obtained from spontaneous reports during post-marketing surveillance, from literature searches performed once weekly using the ProQuest platform, and from ongoing clinical trials.

The SOPs and WOIs outlining details of the Octapharma pharmacovigilance methods are included as Appendices in the US Specific Addendum No. 05 to EU-RMP.

5.1.3 Risk minimization measures

5.1.3.1 Important identified risk: Hypersensitivity reactions, including anaphylactic reactions

As with any plasma-derived protein product administered intravenously, allergic type

hypersensitivity reactions may occur with BALFAXAR. In rare cases, allergic reactions may be life-threatening. *Hypersensitivity reactions, including anaphylactic reactions* are labeled events in the proposed USPI. In addition to routine pharmacovigilance and risk minimization measures included in the proposed USPI (refer to Table 6), no additional risk minimization activities are deemed necessary by the Sponsor.

Reviewer comment

There were no cases of anaphylaxis reported in LEX-204, LEX-205 and LEX-209 but the OSS data includes reports of anaphylaxis that were life-threatening or resulted in death. The Sponsor's plan to add *hypersensitivity reactions, including anaphylactic reactions* as an important identified risk to the PVP is acceptable. Proposed pharmacovigilance activities are acceptable.

5.1.3.2 Important identified risk: Thromboembolic events

Thromboembolic events are serious adverse reactions associated with the use of prothrombin complex concentrates that are potentially life-threatening. *Thromboembolic events* are labeled events in the proposed USPI. In addition to routine pharmacovigilance and risk minimization measures included in the proposed USPI (refer to Table 6), no additional risk minimization activities are deemed necessary by the Sponsor.

Reviewer comment

In the pivotal study LEX-209 four TEEs developed in 3 subjects (one had a pre-existing TEE of mesenteric artery thrombosis and two had prior history of ischemic heart disease/coronary heart disease). Two of the three subjects with TEE died. All TEEs developed within 45 days post-surgery. There were no TEEs reported in the Kcentra group.

In the key supportive study LEX-205, there were 27 TEEs among 14.4% of patients in the *Octaplex* group and 12 TEEs among 9.7% in the FFP group.

The Overview Safety Summary included 66 reports indicative of TEE with 7 fatal outcomes.

There is evidence in the literature suggesting an increased risk of TEEs with PCCs, including *Octaplex* (Song MM et al, 2012, Wozniak M et al, 2012, Riess HB et al., 2007, Salisbury RA., 2014. Williams MS., 2011, Kalus JS., 2013, Kerebel D 2013, Desmetree T 2012, Steiner T 2016).

Also, a numerically higher proportion of subjects experienced events with a fatal outcome in the *Octaplex* group compared with the Kcentra group in LEX-209 (4.8% vs. 1%) and in the *Octaplex* group compared with the FFP group in LEX-205 (20% vs. 13%).

Given the small sample size number in the pivotal study and the observed numerical imbalances in TEEs and deaths observed between *Octaplex* and Kcentra in LEX-209 and between *Octaplex* and FFP in LEX-205, the reviewer recommends that the sponsor also conducts a postmarketing observational study (PMR) to actively monitor TEEs and all-cause mortality in patients treated with BALFAXAR. In the Safety Working Group (SWG) meeting from May 11, 2023, the group supported the need for the PMR should BALFAXAR be approved.

The reviewer considers the summary of the LEX-212 study provided in the US Specific Addendum No.05 to EU-RMP to be acceptable given the sponsor's commitment to making

Proportion of patients with TEEs within 45 days following VKA reversal treatment with BALFAXAR compared to Kcentra the primary study endpoint and Proportion of patients who die from any reason within 45 days following VKA reversal treatment with BALFAXAR compared to Kcentra the secondary study endpoint in the final protocol. DPV will review the full study protocol prior to initiation.

Enhanced pharmacovigilance activities will include submission of all serious and non-serious adverse experience reports for thromboembolic events as 15-day expedited reports and provision of aggregate assessment (based on interval and cumulative data) of TEEs in periodic safety reports in the first three years after licensure.

Proposed pharmacovigilance activities are acceptable.

5.1.3.3 Important identified risk: Heparin induced thrombocytopenia

BALFAXAR contains heparin. *Heparin induced thrombocytopenia* involves the formation of a heparin/platelet factor (PF)-4 complex and the subsequent binding of IgG antibodies. When the immunocomplex IgG-Heparin-PF4 binds the platelet surface this triggers platelet activation / aggregation and subsequent activation of coagulation.

Heparin induced thrombocytopenia is a labeled event in the proposed BALFAXAR USPI. In addition to routine pharmacovigilance and risk minimization measures included in the proposed USPI (refer to Table 6), no additional risk minimization activities are deemed necessary by the Sponsor.

Reviewer comment

The Sponsor's plan to add *heparin induced thrombocytopenia* as an important identified risk to the PVP is acceptable. Proposed pharmacovigilance activities are also acceptable.

5.1.3.4 Important identified risk: Medication dosing errors

The Sponsor has not added medication dosing errors as an important identified risk to the PVP. Incorrect individual dosage calculations can result in overdosing or underdosing, which have important clinical implications.

Reviewer comment

The Sponsor received reports concerning medication dosing errors identified through postmarketing with some of them resulting in death (refer to Section 4.1 of this memo). Medication dosing errors require routine pharmacovigilance (adverse reactions reporting and signal detection). The Sponsor's plan of not including medication dosing errors as an important identified risk to the PVP is not acceptable. The reviewer recommends that the Sponsor includes medication dosing errors as an important identified risk to the PVP. In response to FDA's Jan 23, 2023 IR (received February 3, 2023 as Amendment #013 to STN 125776/0) the sponsor revised the EU-RMP to include medication errors as an important identified risk. Additionally, the US Addendum to the EU-RMP was revised to describe the planned measures for this risk.

Proposed pharmacovigilance activities are acceptable.

5.1.3.5 Important potential risk: Development of neutralizing antibodies / inhibitor development

Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting

one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. The proposed USPI indicates that inhibitors have not been observed in clinical trials. In addition to routine pharmacovigilance and risk minimization measures included in the proposed USPI (refer to Table 6), no additional risk minimization activities are deemed necessary by the Sponsor.

Reviewer comment

The Sponsor's plan to add immunogenicity as an important potential risk to the PVP is acceptable. Proposed pharmacovigilance activities are also acceptable.

5.1.3.6 Important potential risk: Transmission of an infectious agent

Product contamination with infectious agents such as viruses can arise from the donor, or less commonly, from other sources introduced during manufacture (e.g., from the reagents employed). *Transmission of an infectious agent* is a labeled event in the proposed USPI. The proposed USPI acknowledges that standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma may be of limited value against non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19.

In addition to routine pharmacovigilance and risk minimization measures included in the proposed USPI (refer to Table 6), no additional risk minimization activities are deemed necessary by the Sponsor.

Reviewer comment

In LEX-202 (*Efficacy and safety of Octaplex in patients with acquired deficiency of Vitamin K dependent coagulation factors*) there were two conclusive seroconversions to parvovirus B19 7-14 days post last infusion (both subjects received the same batch of *Octaplex*).

In LEX-203 (*Efficacy and safety of Octaplex in patients under oral anticoagulant therapy and undergoing surgery or invasive procedures*) there was one parvovirus B19 infection 3 weeks after Octaplex administration assessed as possibly related to study treatment.

In LEX-006-13-IL (*Efficacy and safety of a prothrombin complex concentrate (Octaplex) for rapid reversal of oral anticoagulation*) three patients became seropositive for parvovirus B-19 11-12 days after treatment. Two of the three subjects had been administered the same batch at the same study site. The Sponsor's plan to add transmission of infectious agents as an important potential risk to the PVP is not acceptable as it should be considered an important identified risk. In response to FDA's Jan 23, 2023 IR (received February 3, 2023 as Amendment #013 to STN 125776/0) the sponsor revised the EU-RMP to reclassify the risk of transmission of an infectious agent as an important identified risk. Additionally, the US Addendum to the EU-RMP was revised to describe the planned measures for this risk.

Proposed pharmacovigilance activities are, otherwise, acceptable.

5.1.4 Risk Evaluation and Mitigation Strategy (REMS) Program

The Sponsor does not propose a REMS for BALFAXAR.

Reviewer comment

The Sponsor's plan of not having a REMS program is acceptable. The labeling and routine and enhanced pharmacovigilance, in addition to a postmarketing requirement safety study to assess TEEs, are adequate for postmarketing safety monitoring.

6. DPV ASSESSMENT

The safety data from the pivotal and key studies conducted in support of this application and from foreign postmarketing surveillance of *Octaplex* are consistent with known events of PCCs and with the events described in the proposed BALFAXAR USPI.

Based on the observed imbalance in TEEs between *Octaplex* and comparator groups in the pivotal and key supportive trials, CBER considers *TEEs* a known serious risk that will be monitored and further assessed in the post-licensure period. CBER will require enhanced pharmacovigilance with submission of all (serious and non-serious) adverse experience reports for thromboembolic events as 15-day expedited reports for 3 years post licensure, should this product be approved.

CBER also considers that the known risk of TEEs needs to be further assessed through a postmarketing observational study. Given the imbalance observed in mortality between the *Octaplex* and comparator groups in the pivotal and key supportive trials, the postmarketing observational study should also evaluate all-cause mortality in patients treated with *Octaplex*. Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA, known in CBER as the Biologics Effectiveness and Safety (BEST) Initiative, is not sufficient to assess this serious risk. An assessment of the sufficiency of the BEST Initiative indicated that its data sources are not sufficient to assess the serious risk of TEEs following treatment with BALFAXAR in lieu of a postmarketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). As per the 2019 draft guidance, Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, this determination “takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug).” At this time, the data sources in the CBER BEST Program are not sufficient to identify the safety outcomes due to uncertainties in product uptake in the post-approval period. Of note, the BEST Program does not include foreign data sources. Since this product is approved outside the U.S. as *Octaplex*, and there is foreign postmarketing use of this product, the sponsor has access to foreign data sources in addition to U.S. data sources, for assessment that are not available in BEST data sources. A finding of insufficiency based on uncertainty at the time of approval is consistent with current Guidance.

Data from the *Octaplex* Overview of Safety Summary (OSS) include reports of hypersensitivity or anaphylaxis that were life-threatening or resulted in death. Proposed pharmacovigilance activities for the important identified risk of hypersensitivity, including anaphylactic reactions are acceptable.

Medication dosing errors have been identified in the postmarketing setting (some resulting in death) and should be included in the PVP as an important identified risk. Medication dosing errors require routine pharmacovigilance (adverse reactions reporting and signal detection).

Transmission of an infectious agent has been documented in clinical trials and should be

included in the PVP as an important identified risk. Transmission of an infectious agent requires routine pharmacovigilance (adverse reactions reporting and signal detection).

The Sponsor's PVP otherwise adequately addresses safety issues identified from clinical trials and post-marketing data and CBER considers the summary of the PMR study included in the US Specific Addendum No.05 to EU-RMP, submitted on May 24, 2023, to be acceptable given the responses of the sponsor to FDA's June 12, 2023 IR (refer to section 5.1 *Safety Issues* of this memorandum)

Final determination of the safety profile of the product used in studies supportive to this BLA is pending the final critical, statistical, and product reviews.

7. DPV RECOMMENDATIONS

Based on the review of the currently available safety data, should product be approved, OBPV/DPV recommends the following actions for post licensure safety surveillance activities:

1. Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80.
2. Enhanced surveillance under 21 CFR 600.80 (c)(1)(i) for TEEs for 3 years following approval:
 - ✓ Submission of all post-marketing reports of TEEs, regardless of seriousness or expectedness, as expedited (15-day) reports
 - ✓ Provision of aggregate assessment (based on interval and cumulative data) of TEEs in periodic safety reports
3. Post marketing requirement (PMR) Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to conduct the following study to assess a known serious risk of TEEs:
 - ✓ Study LEX-212 titled "Observational Study of Safety in Patients Treated with BALFAXAR for Reversal of Vitamin K Antagonist Induced Anticoagulation in Patients Needing Urgent Surgery or Invasive Procedure." This post-marketing, prospective observational study will assess the risk of TEEs following Vitamin K Antagonist (VKA) reversal among patients treated with BALFAXAR or comparator (Kcentra) for reversal of vitamin K antagonist anticoagulation in the setting of urgent surgery or an invasive procedure. Study subjects will be evaluated for the primary endpoint of TEEs within 45 days following VKA reversal treatment with BALFAXAR compared to comparator (Kcentra) and the study will require at least 3574 subjects (1:1 randomization with 1787 patients exposed to BALFAXAR and 1787 patients exposed to the comparator).
 - ✓ The sponsor will submit the full protocol to CBER for review by 12/31/2023

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Appendix 1 Summary of completed clinical studies with *Octaplex*

Study ID	Population	Design/Study Site/Location/ Study Period	Evaluation Criteria	Endpoints
LEX-201	<p>Patients with severe factor II, VII, IX and X deficiency PTPs</p> <p>Age \geq 12 years (mean age 20 years)</p>	<p>Prospective Open-labelled Non-controlled Phase II/III</p> <p>Multi-centre: Poland and Hungary</p> <p>October 1997 to January 1999</p>	<p>PK Efficacy Safety</p>	<p><u>Primary endpoints:</u> PK profile Clinical efficacy in bleeding episodes</p> <p><u>Secondary endpoints:</u> Thrombogenicity Immunogenicity Clinical tolerability (adverse events, vital signs) Viral safety</p>
LEX-202	<p>Patients with major bleeding or surgical or invasive procedures during treatment with anticoagulants of coumarin or indandion type</p> <p>Age \geq 18 years (mean age 68 years)</p>	<p>Prospective Non-randomized Open-labelled Non-controlled Phase II</p> <p>Multi-centre: Israel and Russia</p> <p>July 2000 to February 2001</p>	<p>Efficacy Safety</p>	<p><u>Primary endpoint:</u> Efficacy in correcting prothrombin time</p> <p><u>Secondary endpoints:</u> Recoveries of factor II, VII, IX and X, protein S and protein C Efficacy in bleeding episodes Clinical tolerability (adverse events, vital signs, laboratory safety) Viral safety</p>
LEX-203	<p>Patients receiving anticoagulants of coumarin and indandion type and in whom a surgery or invasive procedure is indicated</p> <p>Age \geq 18 years (mean age 70 years)</p>	<p>Prospective Non-randomized Open-labelled Phase III</p> <p>Multi-center: Germany and Israel</p> <p>November 2003 to July 2005</p>	<p>Efficacy Safety</p>	<p><u>Primary endpoint:</u> Efficacy in correcting prothrombin time</p> <p><u>Secondary endpoints (efficacy):</u> Plasma levels of INR, aPTT and fibrinogen Recoveries of factor II, VII, IX and X and protein C</p> <p><u>Secondary endpoints (safety):</u> Thrombogenicity, Clinical tolerability (adverse events, vital signs, laboratory safety) Viral Safety</p>
LEX-205	<p>Patients under vitamin k antagonist</p>	<p>Prospective Randomised Active controlled</p>	<p>Efficacy Safety</p>	<p><u>Primary endpoints:</u> Correction of INR to <1.5, 15 minutes after the end of first</p>

Study ID	Population	Design/Study Site/Location/ Study Period	Evaluation Criteria	Endpoints
	therapy with the need for urgent surgery or invasive procedures Age ≥ 18 years	Open-labelled Phase III Multi-center: USA 2008 to 2012		infusion of OCTAPLEX or FFP. Number of intra-operative red blood cell units (RBC) transfused <u>Secondary endpoints (efficacy):</u> Intra-operative RBC transfusions, Peri-operative haemostasis assessment PT, aPTT and fibrinogen. Coagulation factor levels. Transfusion requirements other than RBCs Blood losses during and after surgery Change in haematological parameters from the beginning to the end of the surgery /procedure <u>Secondary endpoints (safety):</u> Thrombogenicity Clinical tolerability (adverse events, vital signs, laboratory safety), Viral Safety
LEX-206	Patients with intracranial haemorrhage related to oral anticoagulant therapy. Age ≥ 18 years	Prospective Randomized Open-labelled Phase III Multi-center: France Q3 2008 to Q3 2010	Efficacy Safety	<u>Primary endpoint:</u> INR at 10±5 minutes after the end of injection <u>Secondary endpoints (efficacy):</u> No. of patients with INR ≤ 1.5 at 10±5 min after injection INR, PT, TGA, coagulation factors, protein C, and protein S Haematoma volume Clinical status Global outcome Overall clinical response 48 hours after the end of injection <u>Safety endpoints:</u> Exposure Adverse events, vital signs, laboratory safety
LEX-209	Patients under vitamin k antagonist	Prospective Randomized Active	Efficacy Safety	<u>Primary endpoint:</u> Haemostatic efficacy rating at the end of surgery

Study ID	Population	Design/Study Site/Location/ Study Period	Evaluation Criteria	Endpoints
	therapy with the need for urgent surgery Age ≥ 18 years	controlled Double blinded Phase III Multi-center: USA, Romania, Russia, Ukraine, Belarus and Georgia Q3/2017 to Q4/2021		<u>Secondary endpoints (efficacy):</u> No. of patients with INR ≤ 1.5 at 30 ±15 min after the end of infusion Change in coagulation factor levels from baseline to 30 ±15 min after the end of infusion No. of patients receiving red blood cells during the surgery <u>Safety endpoints:</u> Adverse events Thromboembolic events (overall, within 2, 21 and 45 days after end of surgery) Mortality (overall, within 2, 21 and 45 days after end of surgery) Vital signs, laboratory safety and viral safety

Appendix 2. Summary of LEX-212 study (from US Specific Addendum No.05 to EU-RMP)

<p>Study short name and title: LEX-212 – Observational Study of Safety in Patients Treated With BALFAXAR® for Reversal of Vitamin K Antagonist Induced Anticoagulation in Patients Needing Urgent Surgery or Invasive Procedure</p>
<p>Rationale and study objectives: This prospective observational cohort study is designed to obtain product safety information from the routine clinical setting within large, diverse, community-based populations. The primary objective of this study is to investigate the rate of thromboembolic events and the rate of 45-day, all-cause mortality of BALFAXAR compared to Kcentra in patients under VKA therapy with the need for urgent surgery/invasive procedures. (*)</p>
<p>Study design: Observational cohort study</p>
<p>Study population: Adults admitted to the hospital for an urgent surgery or invasive procedure requiring urgent reversal of VKA treatment with 4F-PCC (BALFAXAR or Kcentra).</p>
<p>Safety concerns addressed: Thromboembolic events</p>
<p>(**) Milestones: Protocol submission: Q4 2023 Study initiation: Q2 2024 Study completion: Q4 2031 Submission of final report: Q2 2032</p>

(*) In response to FDA's June 12, 2023 IR (received June 15, 2023 under STN 125776/0, Amendment #042) the sponsor agreed to making *Proportion of patients with TEEs within 45 days following VKA reversal treatment with BALFAXAR compared to Kcentra the primary study endpoint* and *Proportion of patients who die from any reason within 45 days following VKA reversal treatment with BALFAXAR compared to Kcentra* the secondary study endpoint in the final protocol.

(**) In response to FDA's June 12, 2023 IR (received June 15, 2023 under STN 125776/0, Amendment #042) the sponsor confirmed the following study milestones:

Estimated protocol submission date: 12/31/2023
Estimated study initiation date: 06/30/2024
Estimated study completion date: 12/31/2031
Estimated final report submission date: 06/30/2032