

Applicant: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Pharmacology/Toxicology
Division of Pharmacology/Toxicology 1
Pharmacology/Toxicology Branch 1

BLA NUMBER: STN #125776.000

DATE RECEIVED BY CBER: July 28, 2022

DATE REVIEW COMPLETED: July 11, 2023

PRODUCT: BALFAXAR (Octaplex or Prothrombin Complex Concentrate [human])

APPLICANT: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

PROPOSED INDICATION: 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.

PHARM/TOX REVIEWER: Rondine Allen

PHARM/TOX TEAM LEADER: Christopher Saeui

PHARM/TOX BRANCH CHIEF: Abigail Shearin

PRODUCT (CMC) REVIEWERS: Ze Pen (Chair), Zuben Sauna

CLINICAL REVIEWERS: Karl Kasamon

PROJECT MANAGER: Eden Chane

OFFICE DIRECTOR: Iwen Wu

EXECUTIVE SUMMARY:

BALFAXAR (Octaplex or Prothrombin Complex Concentrate [human]) is a human plasma-derived prothrombin complex concentrate comprised of human coagulation Factors II, VII, IX, X, as well as Protein C and Protein S. The nonclinical *in vitro* and *in vivo* pharmacology, distribution, and toxicology data to support this biologics licensing application (BLA) are summarized below.

The reversal of Phenprogamma® 3-induced anticoagulation was evaluated in a study comparing BALFAXAR to Beriplex (human prothrombin complex) in (b) (4) rats. Following pretreatment with Phenprogamma®, intravenous administration of 500 IU of BALFAXAR or

Applicant: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Beriplex increased concentrations of Factors II, IX, Protein S and Protein C, normalized bleeding time and the international normalized ratio (INR), a standardized measure of blood clotting time and clot stability, and increased the thromboplastin time (TPT) in comparison to saline-administered control animals.

Nonclinical *in vitro* and *in vivo* studies evaluated the risk for BALFAXAR to cause thrombosis. The thrombogenic potential, activity, and concentration of activated coagulation Factors II, VII, IV, and X were determined for heparin-(b) (4) batches of BALFAXAR. Thrombogenic potential was evaluated by determining the partial thromboplastin time, thrombin generation time (TG₅₀), non-activated partial thromboplastin time (NAPTT), and thrombin fibrinogen coagulation time. BALFAXAR was considered non-thrombogenic in each thrombogenicity test. (b) (4)

for all BALFAXAR batches.

The Wessler stasis test¹ was used to evaluate thrombus formation in rats (Report No. Dec 1996) following infusion of 100 IU/kg, 200 IU/kg, and 400 IU/kg of BALFAXAR 500 IU. Thrombogenic scores for (b) (4) and heparin containing batches of BALFAXAR were below the thrombogenic threshold. Three additional studies were conducted in rabbits (Report Nos. 26621/49, 30503, and 37157) to determine the thrombogenic potential of BALFAXAR using the Wessler stasis test. No thrombosis was observed for BALFAXAR 500 or 1000 IU when intravenously administered at 400 IU/kg.

Two studies (Report Nos. SL-LT-221/11 and 37158) were conducted to evaluate local skin reactions to BALFAXAR 500 IU following (b) (4) intravenous administration, or (b) (4) in rabbits. No test article-related macroscopic changes were reported in either study.

Animal reproductive and developmental toxicity and carcinogenicity studies were not conducted with BALFAXAR, which is acceptable based on the product type, safety profile, and proposed indication.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies in the pharmacology and toxicology studies or outstanding information requests for BALFAXAR. The nonclinical data provided in the BLA submission supports approval of this biologics license application.

Formulation and Chemistry:

BALFAXAR (Octaplex) is a human plasma-derived prothrombin complex concentrate comprised of human coagulation Factors II, VII, IX, X, as well as Protein C and Protein S. The (b) (4) will be (b) (4). It is supplied as a lyophilized powder for reconstitution prior to intravenous administration. Octaplex will be available at concentrations of

¹ Wessler S, Reimer SM, Sheps MC. 1959. Biologic assay of a thrombosis-inducing activity in human serum. J Appl Physiol 14:943-6.

500 Factor IX IU in 20 mL (protein content (b) (4) /vial) or 1000 Factor IX IU in 40 mL ((b) (4) /vial) reconstitution volume per vial. Doses will be prepared and reconstituted with a Nextaro® transfer device. The final concentration of each coagulation factor following reconstitution is listed in **Table 1**.

Octaplex is formulated with (b) (4) heparin ((b) (4)) and sodium citrate (b) (4) are present. (b) (4) are used during the manufacturing process for (b) (4) The maximum single dose of 80 IU/kg of Octaplex will result in administration of (b) (4) (b) (4) a total of (b) (4) of heparin/kg, and (b) (4) of sodium citrate/kg.

Table 1: Octaplex coagulation factor specification

Factor	IU/mL
II	(b) (4)
VII	
IX	
X	
Protein S	
Protein C	

Abbreviations

aPTT	Activated Partial Thromboplastin Time
E	Extinction
FEIBA	Factor Eight Inhibitor Bypassing Activity
FFP	Fresh Frozen Plasma
INR	International Normalized Ratio
IU	International Units
IV	Intravenous
kg	Kilogram
NAPTT	Non-Activated Partial Thromboplastin Time
No.	Number
NOAEL	No-observed-adverse-effect-level
PCC	Prothrombin Complex Concentrate
PT	Prothrombin Time
TG _{t50}	Thrombin Generation Time
(b) (4)	(b) (4)
TPT	Thromboplastin Time

Related Files

IND (b) (4) (b) (4)

Table of Contents

INTRODUCTION	4
NONCLINICAL STUDIES.....	5
PHARMACOLOGY STUDIES	5
Summary List of Pharmacology Studies.....	5
Overview of Pharmacology Studies.....	6
SAFETY PHARMACOLOGY STUDIES	8
PHARMACOKINETIC STUDIES.....	15
TOXICOLOGY STUDIES.....	15
Summary List of Toxicology Studies	15
Overview of Toxicology Studies	16
ADDITIONAL SUPPORTING STUDIES.....	19
APPLICANT'S PROPOSED LABEL.....	22
CONCLUSION OF NONCLINICAL STUDIES	23
KEY WORDS/TERMS	23

INTRODUCTION

The coagulation cascade involves a series of reactions catalyzed by coagulation factors. The prothrombin complex is comprised of coagulation Factors II, VII, IX, and X synthesized in the liver and the required co-factor Vitamin K. Factor VII is a zymogen or inactive precursor requiring cleavage by serine protease to Factor VIIa to initiate the blood coagulation pathway. Factor VIIa leads to activation of Factors IX and X to Factors IXa and Xa. Factor II (prothrombin) is also activated and transformed to thrombin (Factor IIa), which leads to the conversion of fibrinogen to fibrin, resulting in clot formation.

Individuals on oral anticoagulants in need of surgical intervention have high risk for uncontrolled bleeding during surgery due to iatrogenic Vitamin K-dependent coagulation factor deficiency. To rapidly reverse the effects of anticoagulants during emergencies, Vitamin K, fresh frozen plasma (FFP), or a currently available human prothrombin complex concentrate (PCC)

administration is recommended to normalize the patient's INR. However, use of Vitamin K or FFP for normalizing INR are not optimal, as complete INR normalization with Vitamin K occurs 24-48 hours post administration,² and FFP requires ABO blood typing and large volumes may be needed, leading to fluid overload and adverse events.

BALFAXAR is a human PCC containing coagulation Factors FIX, FII, FVII, FX, and anticoagulant Protein C and Protein S, along with low concentrations of heparin. BALFAXAR is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist therapy in adult patients with a need for an urgent surgery/invasive procedure. Administration of BALFAXAR is intended to reverse the effects of oral anticoagulant therapy by supplementing deficient coagulation cascade factors.

NONCLINICAL STUDIES

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology study was conducted to support the rationale for the administration of BALFAXAR (also named Octaplex and PPSB [Prothrombin Complex Concentrate] in the nonclinical studies) to treat the proposed clinical indication.

In Vivo Studies

In Vivo Studies in Healthy Animals

Study Number	Study Title / Publication Citation	Report Number
1	Pharmacodynamic study of Octaplex versus Beriplex after single intravenous administration to male (b) (4) rats	33528

Note: Study No. 1 is briefly summarized in this review memo under 'Overview of Pharmacology Studies.'

² Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. 2003. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 163:2469-73.

Overview of Pharmacology Studies*Overview of In Vivo Studies***In Vivo Studies in Healthy Animals****Study #1**

Report Number	33528	
Date Report Signed	15 Dec 2016	
Title	Pharmacodynamic Study of Octaplex Versus Beriplex After Single Intravenous Administration to Male (b) (4) Rats	
GLP Status	<p>Yes Good Laboratory Practice Regulations of the European Commission enacted in Germany in the 'Chemikaliengesetz' [Chemicals Act], current edition;</p> <p>OECD Principles of Good Laboratory Practice' Document No. 1 (ENV/MC/CHEM (98) 17) regulated in the Directive 2004/1 O/EC of the European Parliament and the Council of 11 February 2004.</p>	
Testing Facility	(b) (4)	
Objective(s)	To investigate the reversal of the effect of oral anticoagulant phenprocoumon (Phenprogamma® 3) in rats after a single intravenous injection of Octaplex or PCC Beriplex.	
Study Animals	Strain/Breed	(b) (4) rats
	Species	(b) (4)
	Age	62 days
	Body Weight	260.5 g - 305.1 g
	#/sex/group	10/males/group
	Total #	40
Test Article(s)	Octaplex 500 IU (Batch No. K621B281/V1)	
Control Article(s)	<p>Beriplex P/N 500 (Batch Nos. G5260111C and G7511011)</p> <p>Note: Beriplex is a human PCC containing coagulation Factors II, VII, IX, and X, and anticoagulant Proteins C and S. Beriplex is licensed in the United States for the reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients with need for an urgent surgery/invasive procedure.</p>	
Route of Administration	IV injection	
Description of the Disease/Injury Model	Rats were pretreated with 2.5 mg/kg of Phenprogamma® 3 by oral gavage on test days -2 and -1.	
Study Groups and Dose Levels	<p>Group 1 – Pre-treatment/treatment: saline/saline</p> <p>Group 2 – Pre-treatment/treatment: 2.5mg/kg of Phenprogamma® 3/ Saline</p> <p>Group 3– Pre-treatment/treatment: 2.5mg/kg of Phenprogamma® 3/ Octaplex 40 IU/kg</p> <p>Group 3– Pre-treatment/treatment: 2.5mg/kg of Phenprogamma® 3/ Beriplex 40 IU/kg</p>	
Dosing Regimen	Single IV injection on Day 1	
Randomization	Yes	
Description of Masking	Not provided	
Scheduled Sacrifice Time Points	After determination of bleeding time	

Key Evaluations and Assessments:

Clinical observations:

- Mortality- twice daily
- Body weight- at the time of group assignment, pre-treatment, and on day of test article administration

Blood collection-before test article administration and 15 minutes after test article administration

- Hemoglobin content - platelet count
- Coagulation parameters - (Prothrombin time (PT), thromboplastin time (TPT), INR, Activated partial thromboplastin time (aPTT))
- Coagulation factors - Factor II, Factor VII, Factor IX, Factor X, Protein S, Protein C

Bleeding time- 20 minutes after test article administration. Bleeding time was determined using a method similar to Booth et.al.³

Key Results:

- There were no differences in hemoglobin content between rats dosed with Octaplex, Beriplex, and saline.
- Pretreatment with Phenprogamma® 3 reduced plasma concentrations of Factor II, Factor VII, Factor IX, and Factor X in Groups 2, 3, and 4 when compared to Group 1 animals at the same time point and test day -3 values within each group. There was an increase in Protein C concentration in Groups 2, 3, and 4 following Phenprogamma® 3 pretreatment when compared to Group 1 and test day -3 values within each group.
- Administration of 40 IU/kg Octaplex 500 IU (Group 3) or 40 IU/kg Beriplex (Group 4) resulted in increased concentrations of Factor II, Factor IX, Protein S and Protein C 15 minutes after administration when compared to Group 2. Plasma levels of Factor IX and Factor VII increased slightly following administration of Octaplex 500 IU (Group 3) or Beriplex (Group 4). However, levels of Factor IX and Factor VII were well below Group 1 levels at the same timepoint.
- Pretreatment with Phenprogamma® 3 increased INR, TPT, and aPTT values when compared to test day -3 values and Group 1 on test day 1.
- Administration of Octaplex 500 IU (Group 3) or Beriplex (Group 4) normalized INR and TPT values to levels observed in Group 1.
- Levels of aPTT remained elevated following administration of Octaplex 500 IU (Group 3) and Beriplex (Group 4) when compared to test day 1 values.

³ Booth BP, Jacob S, Bauer JA, Fung HL. 1996. Sustained antiplatelet properties of nitroglycerin during hemodynamic tolerance in rats. J Cardiovasc Pharmacol 28:432-8.

- Administration of Octaplex 500 IU (Group 3) and Beriplex (Group 4) normalized bleeding time to levels observed in Group 1.

Reviewer's Conclusion:

- Octaplex was comparable to Beriplex in reversing the anticoagulant effects of phenprocoumon, normalizing the INR, and increasing the concentrations of Factor II, Factor IX, Protein S, and Protein C following administration of 40 IU/kg to rats.

SAFETY PHARMACOLOGY STUDIES

The following safety pharmacology studies were conducted with Octaplex.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
2	<i>In-vitro</i> and <i>In-vivo</i> Studies Investigating the Thrombogenicity of PPSB (Prothrombin Complex Concentrate) human 500	Dec 1996

Note: Study No. 2 is reviewed with Study No. 3 below.

In Vivo Studies

***In Vivo* Studies in Healthy Animals**

Study Number	Study Title / Publication Citation	Report Number
3	<i>In-vitro</i> and <i>In-vivo</i> Studies Investigating the Thrombogenicity of PPSB (Prothrombin Complex Concentrate) human 500	Dec 1996
4	Examination of Octaplex on Thrombogenic Risk in Rabbits After Intravenous Administration	26621/49
5	Examination of Octaplex Preparations for Thrombogenic Properties in Rabbits after Intravenous Administration	30503
6	Examination of Octaplex 500 for Thrombogenic Properties in Rabbits after intravenous Administration	37157

Note: Study Nos. 2-6 are briefly summarized in this review memo under 'Overview of Safety Pharmacology Studies.'

Overview of Safety Pharmacology Studies

Study #3

Report Number: Dec 1996

Study Title: *In-vitro* and *In-vivo* Studies Investigating the Thrombogenicity of PPSB (Prothrombin Complex Concentrate) human 500

Objective: To assess the thrombogenic potential of prothrombin complex concentrates (Thrombin Fibrinogen Coagulation Time, Thrombin Generation Time (TGt₅₀), Non-activated Partial Thromboplastin Time (NAPTT), (b) (4) (b) (4) heparin *in vitro* and *in vivo*.

Note: Octaplex (BALFAXAR) is referred to as PPSB throughout the study report.

Methods (*in vitro*):

- Thrombin Fibrinogen Coagulation Time
(b) (4)
- Thrombin Generation Time (TGt₅₀)
(b) (4)
- Non-activated Partial Thromboplastin Time (NAPTT)
(b) (4)
- (b) (4)
(b) (4)
(b) (4)
- (b) (4)
(b) (4) (b) (4)
- (b) (4)
(b) (4) (b) (4)

Key Results (*in vitro*):

- Thrombin Fibrinogen Coagulation Time
 - No fibrin generation occurred in heparin (b) (4) of Octaplex in the thrombin fibrinogen coagulation time assay.

⁴(b) (4)

⁵(b) (4)

- Thrombin Generation Time (TGt50)
 - It was not possible to calculate the thrombin generation time because no coagulation was observed within (b) (4) in heparin (b) (4) preparations.
- NAPTT
 - None of the of Octaplex formulations showed thrombogenic potential in the NAPTT assay.
- (b) (4)
 - (b) (4)

(b) (4)

(b) (4)

(b) (4)

Methods (*in vivo*):

GLP Status	No	
Testing Facility	(b) (4)	
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	Not provided
	Body Weight	Not provided
	#/sex/group	2-4/Females/group
	Total #	28
Test Article(s)	<p>Three batches of Octaplex with heparin were tested. The Factor IX content was 500 IU/vial and heparin content was (b) (4) (Batch Nos: 60 800 4265, 60 300 2265, 55 000 6265)</p> <p>Two (b) (4) batches of Octaplex were tested (Batch No. 608003265 and 603001265)</p> <p>Note: Octaplex (BALFAXAR) is referred to as PPSB throughout the study report.</p>	
Control Article(s)	<p>Positive control: Human serum activated with kaolin</p> <p>Negative control: Saline solution</p>	

Route of Administration	Intravenous injection into the femoral artery
Description of the Disease/Injury Model and Implant Procedure	Wessler Stasis Model ¹ : Prior to administration of Octaplex, the left and right jugular veins were prepared for ligation. Octaplex was administered to the femoral artery. Blood flow was occluded in the left and right jugular veins 30 seconds after Octaplex administration. After 20 minutes, the jugular vein segment was resected and scored.
Study Groups and Dose Levels	Group 1 – Octaplex with heparin (400 IU/kg) Group 2 – Octaplex (b) (4) (200 IU/kg or 100 IU/kg) Group 3 – Octaplex with heparin (400 IU/kg or 200 IU/kg) Group 4 – Octaplex (b) (4) (200 IU/kg or 100 IU/kg) Group 5 – Octaplex with heparin (400 IU/kg) Group 6 – Human serum (kaolin activated; 1.32 mL/kg) Group 7 – Saline
Dosing Regimen	Single injection
Randomization	No
Description of Masking	Not provided
Scheduled Sacrifice Time Points	20 minutes after Octaplex administration

Reviewer's Notes:

- Octaplex includes coagulation factors that are procoagulant. Therefore, there is a risk of thrombotic events.
- Heparin is included in the formulation to reduce the risk of clotting protein activation.

Key Evaluations and Assessments:

- Resected jugular veins were evaluated for thrombus formation using a scoring scale from 0 to 4 (**Table 2**) after a stasis time of 10 minutes.

Table 2: Description of scale used to score clot formation

Score	Description
0	No thrombus generation
1	Some macroscopically visible fibrin fibers, small thrombus
2	Some small thrombi
3	Two or more larger thrombi or one larger thrombus that does not fill the entire vascular segment
4	One large thrombus filling out the vascular segment

Key Results (in vivo):

- Thrombus formation
 - The average scores for all heparin (b) (4) batches of Octaplex were below the thrombogenic threshold of 2. The positive control (kaolin activated serum) was assigned a mean score of 3.5.
 - Batches (b) (4) (200 IU/kg and 100 IU/kg), were assigned a mean score of 1.83 (Batch 60 800 3265) and 1.67 (100 IU/kg; Batch 60 300 1265).
 - Batches with heparin (400 IU/kg) were assigned a mean score of 1.5 (Batch 60 800 4265) and 0 (Batch 55 000 6265).

Reviewer's Conclusion:

- Under the test conditions used, the risk of Octaplex-induced thrombosis appears low. In each batch of Octaplex evaluated, the content of (b) (4) Factors (b) (4) were low or undetectable. However, this study did not assess the risk of thrombosis formation when the INR is elevated *in vivo*, such as in the clinical setting.

Study #4

Report Number	26621/49	
Date Report Signed	10 Feb 2012	
Title	Examination of Octaplex on Thrombogenic Risk in Rabbits After Intravenous Administration	
GLP Status	Yes §19b Abs. 1 Chemikaliengesetz	
Testing Facility	(b) (4)	
Objective(s)	To examine the thrombogenic risk of Octaplex in rabbits after intravenous (IV) injection.	
Study Animals	Strain/Breed	(b) (4) rabbit
	Species	(b) (4)
	Age	3 months old
	Body Weight	2.2 – 2.5 kg
	#/sex/group	5 males/group
	Total #	25
Test Article(s)	Octaplex (Batch Nos. B124B261/D, E124B265/D, A125A261/U) Note: Octaplex is referred to as Octaplex 500 IU, Octaplex, Charge, and Octaplex Cup no. 1439 throughout the study report.	
Control Article(s)	Positive control: Factor Eight Inhibitor Bypassing Activity (FEIBA) (Batch No. VNF2L018) Negative control: Saline (Batch (b) (4))	
Route of Administration	IV injection	
Description of the Disease/Injury Model and Implant Procedure	Rabbits were anesthetized, and the structures and tributaries to the external jugular vein were ligated with a suture. Octaplex was administered into the marginal vein of the ear. Within 25 seconds of injection of Octaplex, the jugular vein was clamped for 10 minutes. The clamped jugular vein segment was excised with the clamps and examined.	
Study Groups and Dose Levels	Group 1 – Octaplex 500 IU (Batch No. B124B261/D)- 400 IU/kg Group 2 – Octaplex, (Batch No. E124B265/D)- 400 IU/kg Group 3– Octaplex Cup no. (Batch No. A125A261/U)- 400 IU/kg Group 4 – Saline Group 5–FEIBA- 30 U/kg	
Dosing Regimen	Single IV injection	
Randomization	No	
Description of Masking	Not provided	
Scheduled Sacrifice Time Points	Maximum of 15 minutes after administration of anesthesia and Octaplex	

Key Evaluations and Assessments:

- Thrombogenic risk was determined based on the assay reported in Wessler et.al.¹ Resected veins were evaluated for thrombus formation using a scoring scale from 0 to 4 (**Table 2**, above) after a stasis time of 10 minutes.

Key Results:

- Octaplex did not show any thrombogenic effect at 400 IU/kg under test conditions (mean score: 0.0). The mean score for 5 out of 5 animals in the positive control group was 4, indicating a single thrombus forming a cast of the isolated segment.

Reviewer's Conclusion:

- No thrombosis was observed for multiple batches of Octaplex in the Wessler stasis test when administered at 400 IU/kg to rats.

Study #5

Report Number		30503
Date Report Signed		21 Nov 2013
Title		Examination of Octaplex Preparations for Thrombogenic Properties in Rabbits After Intravenous Administration
GLP Status		Yes Good Laboratory Practice according §19b Abs. 1 Chemikaliengesetz
Testing Facility		(b) (4)
Objective(s)		To examine the thrombogenic potential of Octaplex in rabbits after IV injection.
Study Animals	Strain/Breed	(b) (4) rabbit
	Species	(b) (4)
	Age	3 months old
	Body Weight	2.2 – 2.5 kg
	#/sex/group	5 males/group
	Total #	25
Test Article(s)		Octaplex 1000 IU / Expiration date: 36 months (Batch No. D029011008261) Octaplex 1000 IU / Expiration date: 36 months (Batch No. D029021008261) Plex-1000/ Expiration date: 36 months (Batch No. B023B 261/DL085011008261) Plex-1000/ Expiration date: 36 months (Batch No. B023B 261/D 085021008261) Note: Octaplex is referred to as Octaplex 1000 IU and Plex-1000 throughout the study report.
Control Article(s)		N/A
Route of Administration		IV injection
Description of the Disease/Injury Model and Implant Procedure		Rabbits were anesthetized and the structures and tributaries to the external jugular vein were ligated with a suture. Octaplex was administered into the marginal vein of the ear. Within 25 seconds of injection of Octaplex, the jugular vein was clamped for 10 minutes. The clamped jugular vein segment was excised with the clamps and examined.

Study Groups and Dose Levels	Group 1 – Octaplex 1000 IU (Batch No. D029011008261)- 400 IU/kg Group 2 – Octaplex 1000 IU (Batch No. D029021008261)- 400 IU/kg Group 3– Plex-1000 (Batch No. B023B 261/DL085011008261)- 400 IU/kg Group 4 – Plex-1000 (Batch No. B023B 261/DL085021008261)- 400 IU/kg
Dosing Regimen	Single IV injection
Randomization	Yes
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Maximum of 15 minutes after administration of anesthesia and Octaplex

Key Evaluations and Assessments:

- Resected veins were evaluated for thrombus formation using a scoring scale from 0 to 4 (**Table 2**, above) after a stasis time of 10 minutes.

Key Results:

- The mean score of rabbits administered Octaplex 1000 IU or Plex-1000 was 0 indicating no thrombogenic effect under the test conditions.

Reviewer's Conclusion:

- In the Wessler stasis test conducted using rabbits, no thrombosis was observed following administration of 400 IU/kg of Octaplex 1000 IU.

Study #6

Report Number	37157	
Date Report Signed	18 Apr 2019	
Title	Examination of Octaplex 500 for Thrombogenic Properties in Rabbits After intravenous Administration	
GLP Status	Yes Good Laboratory Practice Regulations of the European Commission enacted in Germany in the 'Chemikaliengesetz' [Chemicals Act], current edition; OECD Principles of Good Laboratory Practice' Document No. 1 (ENV/MC/CHEM (98) 17) regulated in the Directive 2004/1 O/EC of the European Parliament and the Council of 11 February 2004.	
Testing Facility	(b) (4)	
Objective(s)	To examine the thrombogenic properties of Octaplex in rabbits after IV injection.	
Study Animals	Strain/Breed	(b) (4) rabbit
	Species	(b) (4)
	Age	9 months old
	Body Weight	1.8-2.2 kg
	#/sex/group	5 males/group
	Total #	25
Test Article(s)	Octaplex 500 IU (Batch No. K849C284/U)	

Control Article(s)	Positive control: Shire FEIBA NF 1000 E (Batch No. F2S088AE) Negative control: saline (Batch No. (b) (4))
Route of Administration	IV injection
Description of the Disease/Injury Model and Implant Procedure	Rabbits were anesthetized and the structures and tributaries to the external jugular vein were ligated with a suture. Octaplex was administered into the marginal vein of the ear. Within 25 seconds of injection of Octaplex, saline, or FEIBA, the jugular vein was clamped for 10 minutes. The clamped jugular vein segment was excised with the clamps and examined.
Study Groups and Dose Levels	Group 1 – Octaplex 500 IU – 400 IU/kg Group 2 – Saline Group 3– Shire FEIBA NF 1000 E
Dosing Regimen	Single IV injection
Randomization	Yes
Description of Masking	Not provided
Scheduled Sacrifice Time Points	Maximum of 15 minutes after administration of anesthesia and Octaplex

Key Evaluations and Assessments:

- Resected veins were evaluated for thrombus formation using a scoring scale from 0 to 4 (**Table 2**, above) after a stasis time of 10 minutes.

Key Results:

- No clot formation, indicated by a mean score of 0, was observed after administration of 400 IU/kg of Octaplex 500 IU or saline. In the positive control group (Group 3), FEIBA produced a single thrombus forming a cast of the isolated segment in all 3 animals with an assigned score of 4.

Reviewer's Conclusion:

- In the Wessler stasis test conducted using rabbits, no thrombosis was observed following administration of 400 IU/kg of Octaplex 500 IU.

PHARMACOKINETIC STUDIES

No pharmacokinetic studies were conducted with Octaplex.

TOXICOLOGY STUDIES**Summary List of Toxicology Studies***Toxicology Studies*

No toxicology studies were conducted for Octaplex. Toxicology studies conducted to evaluate the safety of (b) (4) are reviewed under Additional Supporting Studies.

Developmental and Reproductive Toxicology Studies:

Developmental and reproductive safety studies were not conducted for Octaplex because these evaluations are not required for this product class.

Genotoxicity Studies:

Studies were not conducted to evaluate genotoxicity of Octaplex because this evaluation is not required for this product class.

Carcinogenicity/Tumorigenicity Studies:

Studies were not conducted to assess carcinogenicity of Octaplex because this evaluation is not required for this product class.

Other Safety Studies

Study Number	Study Title / Publication Citation	Report Number
7	"Octaplex 500": Study on Local Tolerance after Intravenous, (b) (4) Administration in Rabbits	SL-LT-221/11
8	Local Tolerance Study of Octaplex 500 Following Single Intravenous, (b) (4) Administration in Rabbits	37158

Overview of Toxicology Studies**Local Tolerance Studies****Study #7**

Report Number	SL-LT-221/11	
Date Report Signed	December 20, 2011	
Title	"Octaplex 500": Study on Local Tolerance After Intravenous, (b) (4) Administration in Rabbits	
GLP Status	Yes OECD principles of Good Laboratory Practice	
Testing Facility	(b) (4)	
Objective(s)	To reveal possible irritative effects of the test items following a single intravenous (b) (4) administration in rabbits.	
Study Animals	Strain/Breed	Rabbits, (b) (4)
	Species	(b) (4)
	Age	Not provided
	Body Weight	2.5-3.4 kg
	#/sex/group	2/sex/group
Total #	36	
Test Article(s)	Octaplex 500 (Batch Nos.: A125A261/U, B124B261/D, E124B265/D)	
Control Article(s)	Water for injection (Batch Nos.: (b) (4))	
Route of Administration	IV infusion	

Study Groups and Dose Levels	Batch No. A125A261/U Group 1 – IV infusion, 2.5 mL/ animal Group 2 – (b) (4) 2.5 mL/ animal Group 3 – (b) (4) 0.1 mL/ animal
	Batch No. B124B261/D Group 4 – IV infusion, 2.5 mL/ animal Group 5 – (b) (4) 2.5 mL/ animal Group 6 – (b) (4) 0.1 mL/ animal
	Batch No. E124B265/D Group 7 – IV infusion, 2.5 mL/ animal Group 8 – (b) (4) 2.5 mL/ animal Group 9 – (b) (4) 0.1 mL/ animal
	Dosing Regimen Single (b) (4) infusion into the right pinna of the ear Water was injected into the contralateral ear
Randomization	No
Description of Masking	Not provided
Scheduled Sacrifice Time Points	96 hours after dosing

Note: Per the applicant, (b) (4) were included because Octaplex 500 could be mistakenly administered by all three routes of administration.

Key Evaluations and Assessments:

- Behavior and physical signs were evaluated 0.5, 1, 2, 6, 24, 48, 72 and 96 hours after Octaplex administration.
- Histopathology assessment (hematoxylin & eosin tissue staining) was performed 96 hours after test article administration.

Key Results:

- Following IV infusion, (b) (4) no Octaplex 500-related findings were reported at the administration site at any timepoint.
- Histopathology, focal (minimal) inflammatory cell infiltration was noted at the test site following (b) (4) administration of Octaplex 500. This finding was considered procedure-related.

Reviewer's Conclusion:

- No test article related findings were reported following IV infusion, (b) (4) (b) (4) of Octaplex.

Study #8

Report Number	37158	
Date Report Signed	December 20, 2011	
Title	Local Tolerance Study of Octaplex 500 Following Single Intravenous, (b) (4) Administration in Rabbits	
GLP Status	Yes Good Laboratory Practice Regulations of the European Commission enacted in Germany in the 'Chemikaliengesetz',	
Testing Facility	(b) (4)	
Objective(s)	To obtain information on the local tolerance of Octaplex 500 in rabbits after a single intravenous, (b) (4) administration.	
Study Animals	Strain/Breed	Rabbits, (b) (4)
	Species	(b) (4)
	Age	5 months old
	Body Weight	Males: 3.87 - 4.59 kg Females: 4.08 - 5.32 kg
	#/sex/group	2/sex/group
Total #	36	
Test Article(s)	Octaplex 500 (Batch No.: K849C284/U)	
Control Article(s)	0.9% NaCl solution	
Route of Administration	IV infusion	
Study Groups and Dose Levels	Group 1 – IV infusion, 2.5 mL/ animal Group 2 – (b) (4) 2.5 mL/ animal Group 3 – (b) (4) 0.1 mL/ animal	
Dosing Regimen	Single (b) (4) or infusion into the right pinna of the ear Water was injected into the contralateral ear	
Randomization	No	
Description of Masking	Not provided	
Scheduled Sacrifice Time Points	96 hours after dosing	

Key Evaluations and Assessments:

- General clinical observations were evaluated before and after administration of Octaplex 500.
- Local reactions were inspected macroscopically 1 h, 2 h, 6 h, 24 h, 48 h, 72, and 96 h after Octaplex 500 administration.

Key Results:

- There were no Octaplex 500 related morphological lesions following intravenous, (b) (4) (b) (4) administration at any timepoint.
- Minimal perivascular hemorrhaging was noted at the test site in one animal 96 hours after IV infusion of Octaplex 500. No other morphological changes were reported at the control site or test site for any other animals. This finding was considered procedure related.

Reviewer's Conclusion:

- No test article related findings were reported following IV infusion, (b) (4) (b) (4) of Octaplex under the study conditions.

ADDITIONAL SUPPORTING STUDIES**Summary list of studies for (b) (4)**

Toxicology studies were conducted to evaluate the safety of (b) (4) which were used for (b) (4) during manufacturing of early batches of Octaplex. The licensed product will be manufactured with (b) (4) therefore, Toxicology Study Nos. 9-15, Developmental and Reproductive Toxicology Study Nos. 16-17, and Genotoxicity Study Nos. 18-19, which are designed to evaluate the safety of (b) (4) (b) (4) are only briefly summarized. The applicant did not conduct any studies with (b) (4) (b) (4) which are used during the manufacturing process for (b) (4) In the final product, (b) (4)

Study Number	Study Title / Publication Citation	Report Number
Toxicology		
9	Acute Toxicity (b) (4) Administration by (b) (4)	7724/92
10	Acute Toxicity (b) (4) Administration to Newborn (b) (4) Rats by (b) (4)	7725/92
11	Examination of the Acute Toxicity of (b) (4) by (b) (4) Administration to (b) (4) Mice	5123/88
12	Examination of the Acute Toxicity of (b) (4) by Intravenous Administration to (b) (4) Rats	6344/90
13	Examination of the Acute Toxicity of (b) (4) by (b) (4) Administration to (b) (4) Rats	5126/88
14	13-week Sub-Chronic Toxicity Study of (b) (4) by Intravenous Administration to (b) (4) Rats	5568/1/89
15	13-week Sub-Chronic Toxicity Study of (b) (4) by Intravenous Administration to (b) (4) Dogs	5569/1/89
Developmental and Reproductive Toxicology		
16	Examination of the Influence of (b) (4) on the Pregnant Rat and the Fetus by Intravenous Administration	6086/90
17	Examination of the Influence of (b) (4) on the Pregnant Rabbit and the Fetus by Intravenous Administration	6087/90
Genotoxicity		
18	(b) (4) <i>in vitro</i> in (b) (4) Cells	November 5 th , 1986
19	(b) (4) Test with the Test Compound (b) (4) – Called (b) (4) – on Bone Marrow Cells of Treated (b) (4) -mice	December 24 th , 1986

Overview of Toxicology Studies with (b) (4)

Study #9, Report No. 7724/92: Acute Toxicity Study of (b) (4) by

(b) (4) Administration

(b) (4)

Study #10, Report No. 7725/92: Acute Toxicity Study of (b) (4) by

(b) (4) Administration to Newborn (b) (4) Rats

(b) (4)

Study #11, Report No. 5123/88: Examination of the Acute Toxicity of (b) (4) by (b) (4)

Administration to (b) (4) Mice

(b) (4)

Study #12, Report No. 6344/90: Examination of the Acute Toxicity of (b) (4) by Intravenous

Administration to (b) (4) Rats

(b) (4)

Study #13, Report No. 5126/88: Examination of the Acute Toxicity of (b) (4) by (b) (4)

Administration to (b) (4) Rats

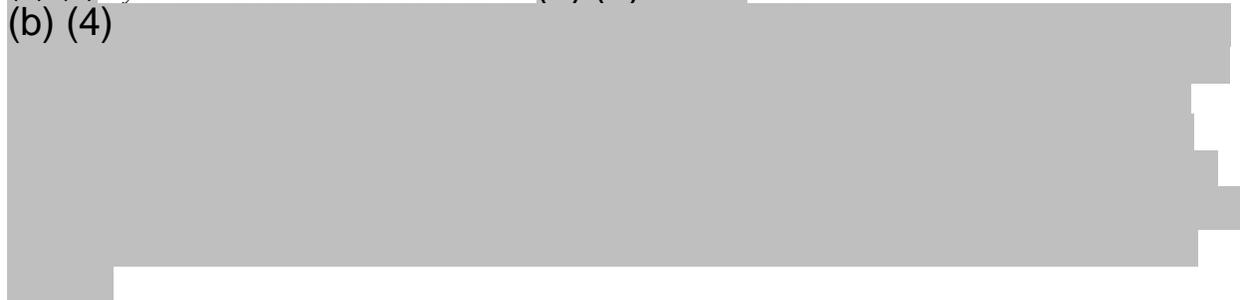
(b) (4)



Study #14, Report No. 5568/1/89: 13-week Sub-Chronic Toxicity Study of (b) (4)

(b) (4) by Intravenous Administration to (b) (4) Rats

(b) (4)



Study #15, Report No. 5569/1/89: 13-week Sub-Chronic Toxicity Study of (b) (4)

(b) (4) by Intravenous Administration To (b) (4) Dogs

(b) (4)



Overview of Developmental and Reproductive Toxicology with (b) (4)

Study #16, Report No. 6086/90: Examination of the influence of (b) (4)

on the pregnant rat and the fetus by intravenous administration

(b) (4)



Study #17, Report No. 6087/90: Examination of the Influence of (b) (4) on the Pregnant Rabbit and the Fetus by Intravenous Administration

(b) (4)



Overview of Genotoxicity with (b) (4)

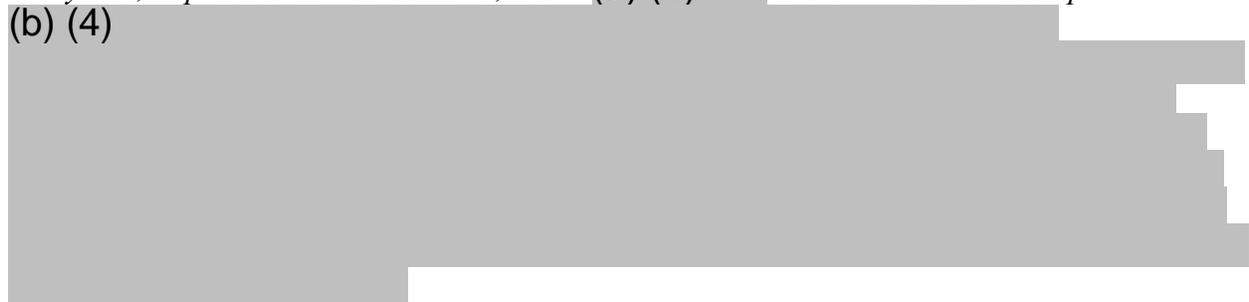
Study #18, Report No. November 5th, 1986: (b) (4) in vitro in (b) (4)

(b) (4)



Study #19, Report No. December 24th, 1986: (b) (4) Test with the Test Compound

(b) (4)



APPLICANT'S PROPOSED LABEL

Section 8 ('Use in Specific Populations') complies with 21 CFR 201.56(d)(1), 201.57(c)(9) and 201.57(c)(14).

Section 13.2 ('Animal Toxicology and/or Pharmacology') is acceptable.

CONCLUSION OF NONCLINICAL STUDIES

Review of the available nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of this biologics license application.

KEY WORDS/TERMS

Coagulation factor deficiency, BALFAXAR®, Octaplex, prothrombin complex concentrate, human coagulation factor, Factor II, Factor VII, Factor IX, Factor, Protein C, Protein S, rabbits, rats.