Balfaxar®
Prothrombin Complex Concentrate, Human-Ians

Balfaxar Formulary Kit

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

Important Safety Information

Balfaxar (prothrombin complex concentrate, human-lans) 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.

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS
Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding. Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Balfaxar in clinical trials and post marketing surveillance. Monitor patients receiving Balfaxar for signs and symptoms of thromboembolic events. Balfaxar may not be suitable in patients with thromboembolic events in the prior 3 months.

Balfaxar is contraindicated in patients with known anaphylactic or severe systemic reactions to Balfaxar or any of its components. Balfaxar is also contraindicated in patients with a known allergy to heparin, a history of heparin-induced thrombocytopenia (HIT), and IgA deficient patients with known antibodies against IgA.

In clinical trials, the most frequent (≥3%) adverse reactions observed in subjects receiving Balfaxar were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting, and catheter-site-related reaction.

Balfaxar is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

Please see full prescribing information, including boxed warning starting on page 22

© 2023 Octapharma USA Inc. All rights reserved.

Table of Contents

1 | Executive Summary **4-6**
1.1 Product Description 4
1.2 Challenges Associated With Warfarin 4
1.3 Benefits of Balfaxar 4
1.4 Pivotal Trial Results 5
1.5 Postmarketing Data 6
1.6 Reimbursement Information 6
2 | Production Information and Disease Description **7-15**
2.1 Product Summary 7
2.2 Product Information 7
2.2.1 Indication and Usage 7
2.2.2 Dosage and Administration 7-8
2.2.3 Manufacturing Information 8
2.3 Disease Description 9
2.3.1 Epidemiology and Relevant Risk Factors 9-10
2.3.2 Pathophysiology 10
2.3.3 Clinical Presentation 11
2.3.4 Disease Burden 11
2.4 Approaches to Treatment 12
2.5 Benefits of Balfaxar 13
2.5.1 Clinical Evidence 13
2.5.1.1 Key Efficacy Findings 13-14
2.5.1.2 Safety outcomes 14
2.5.1.3 Key Product Features – nextaro® 15
3 | Production Comparison Table **16-18**
4 | Additional Clinical Studies **18-19**
4.1 LEX-202: Non-randomized, non-controlled, open-label study 18
4.2 LEX-203: Non-randomized, non-controlled, open-label study 18
4.3 LEX-204: Observational study 18
5 | Conclusion **20**
6 | Postmarketing Study **20**
7 | Reimbursement Information **20**
8| Contact & Ordering Information **21**
9 | Important Safety Information **21**
Appendix A: Prescribing Information **22-28**
Appendix B: References **28-30**

List of Abbreviations

3F-PCC	3-factor prothrombin complex concentrate
4F-PCC	4-factor prothrombin complex concentrate
AE	Adverse event
AHFS	American Hospital Formulary Service
AMCP	Academy of Managed Care Pharmacy
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
ASP	Average sales price
bw	Body weight
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CJD	Creutzfeldt-Jakob disease
CPB	Cardiopulmonary bypass
DOAC	Direct-acting oral anticoagulant
DVT	Deep vein thrombosis
F2D	Factor II deficiency
FDA	Food and Drug Administration
FEIBA	Factor VIII inhibitor bypassing activity
FFP	Fresh frozen plasma
FII	Factor II
FVII	Factor VII
FIX	Factor IX
FX	Factor X
FXa	Activated factor X
HIT	Heparin-induced thrombocytopenia
ICH	Intracranial hemorrhage
INR	International normalized ratio
IU	International unit
IV	Intravenous
MI	Myocardial infarction
NDC	National drug code
NOAC	Non-vitamin K antagonist oral anticoagulant
OAC	Oral anticoagulant
PE	Pulmonary embolism
PPP	Per protocol population
PT	Prothrombin time
PTT	Partial thromboplastin time
RCT	Randomized controlled trial
rFVIIa	Recombinant factor VIIa
SD	Standard deviation
TBI	Traumatic brain injury
TEAE	Treatment emergent adverse events
TEE	Thromboembolic event
TIA	Transient Ischemic attack
US	United States
vCJD	Variant Creutzfeldt-Jakob disease
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WAC	Wholesale acquisition cost

© 2023 Octapharma USA Inc. All rights reserved.

1 | *Executive Summary*

1.1 Product Description

Balfaxar® (prothrombin complex concentrate, human-lans) is a purified, virus-inactivated, nanofiltered, lyophilized, non-activated plasma protein concentrate made from pooled human plasma collected from US donors. It contains blood coagulation Factors II, VII, IX, and X, as well as antithrombotic Proteins C and S. Balfaxar is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA (e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.

Balfaxar provides several key advantages[1]

- Effective hemostasis and fast INR reduction
- Similar efficacy and safety to Kcentra® in a head-to-head clinical trial
- Stable at room temperature for 8 hours after reconstitution
- Includes the user-friendly nextaro® transfer device
- No thawing or ABO typing required before administration

Dosing of Balfaxar is determined using the patient's baseline international normalized ratio (INR) and body weight. Vitamin K should be administered concurrently, through a separate infusion line, to patients receiving Balfaxar to maintain factor levels once the effects of Balfaxar have diminished.

1.2 Challenges Associated With Warfarin

Warfarin is commonly used for the long-term prevention and treatment of a variety of thromboembolic (TE) disorders in patients with atrial fibrillation, prosthetic heart valves, or venous thromboembolism.[2] VKAs inhibit the synthesis of functional vitamin K–dependent coagulation factors (II, VII, IX, and X), thereby reducing the risk of TE events; they also reduce vitamin K–dependent antithrombotic Proteins C and S.[2] Although warfarin is a highly effective antithrombotic agent, it has some limitations. Dose adjustment and close monitoring are necessary based on individual patients' characteristics. Despite regular monitoring, however, bleeding is the primary complication in these patients and can contribute significantly to patient mortality.[3,4]

Kcentra is a registered tradelmark of CSL Behring GmbH
nextaro is a registerd trademark of sfm medical devices GmbH

Immediate reversal of anticoagulation is desirable for the management of VKA-treated patients experiencing acute major bleeding, particularly if the bleeding is life-threatening, or if the patient requires urgent surgery or an invasive procedure. Guidelines recommend the utilization of 4-factor prothrombin complex concentrate (4F-PCC) and vitamin K for the rapid reversal of VKAs[5,6,7].Notably, guidelines favor non-activated 4F-PCC over FFP and 3-factor prothrombin complex concentrate (3F-PCC) in these scenarios.

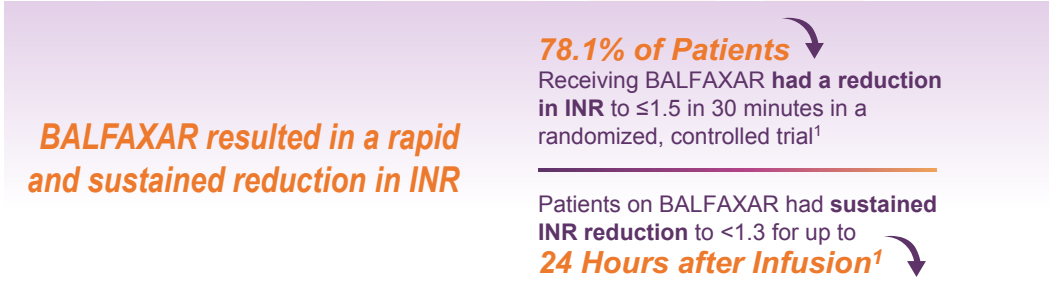


Figure 1

1.3 Benefits of Balfaxar

Balfaxar, is a non-activated 4F-PCC that is an alternative to Kcentra for adult patients in need of the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists (e.g. warfarin) for an urgent surgery or an invasive procedure. In a randomized, double-blind, multicenter study in comparison to Kcentra, for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery, Balfaxar demonstrated non-inferior hemostatic efficacy and early sustained INR reduction. The relationship between INR values and clinical hemostasis in patients has not been established.

© 2023 Octapharma USA Inc. All rights reserved.

1.4 Pivotal Trial Results[1,42]

Efficacy

The efficacy of Balfaxar was assessed in a randomized, double-blind, multicenter study in comparison to Kcentra, for the reversal of vitamin K antagonist induced anticoagulation in adult patients needing urgent surgery. A total of 208 subjects with acquired coagulation factor deficiency due to oral Vitamin K antagonist therapy were randomized to a single dose of Balfaxar (n=105) or Kcentra (n=103). The primary effectiveness endpoint was the non-inferiority of Balfaxar compared to Kcentra. INR reduction to ≤1.5 at 30 minutes post-infusion; plasma levels of Factor II (FII), Factor VII (FVII), Factor IX (FIX), Factor X (FX), and proteins C and S; and treatment emergent adverse events (TEAEs) were select secondary and safety endpoints. Balfaxar demonstrated non-inferiority (primary study objective) compared with Kcentra in achieving hemostatic efficacy (see below).

Rating of Hemostatic Efficacy in Urgent Surgery RCT

Effective hemostasis	No. (%) of subjects		Proportion difference BALFAXAR vs. Kcentra
	BALFAXAR	Kcentra	
Interim analysis	88/93 (94.6%)	86/92 (93.5%)	1.1%, 98% CI: (-9.2%, 11.5%)*
Final analysis**	99/105 (94.3%)	97/103 (94.2%)	0.1%, 95% CI: (-8.0%, 8.2%)

CI = confidence interval N = number of subjects
*Met pre-specified non-inferiority criterion (Margin used -15% and p<0.001, statistically significant at pre-specified alpha level of 0.01)
**Descriptive analysis of all subjects in the study including an overrun of subjects during the decision making at the interim analysis.

The proportion of patients achieving an INR ≤1.5 as measured 30 minutes after the end of the infusion was 78.1% in the Balfaxar group versus 71.8% in the Kcentra group (proportion difference of 6.3%; 95% CI: -5.5%, 18.0%). Overall, 72.1% of patients had vitamin K administered, with a median dose of 10 mg in both groups (see below).

Decrease of INR (to 1.5 or Less at 30 Minutes after End of Infusion) in Urgent Surgery RCT

Rating	No. (%) of subjects		Proportion difference BALFAXAR vs. Kcentra (95% CI for difference)
	BALFAXAR (N=105)	Kcentra (N=103)	
Decrease of INR to ≤ 1.5 at 30 min	82 (78.1)	74 (71.8)	6.3% (-5.5%, 18.0%)

Safety

Based on the results of the phase 3 randomized controlled trial in subjects with acquired coagulation factor deficiency due to VKA therapy, Balfaxar demonstrated a safety profile similar to Kcentra.

There were three subjects (2.9%) with Balfaxar who experienced four thromboembolic events in the randomized controlled trial in urgent surgery; cerebral infarction, pulmonary embolism, unstable angina and myocardial ischemia. The number of thromboembolic adverse reactions assessed as at least possibly related to study treatment was one (1%) with Balfaxar (unstable angina).

There is a risk of thrombosis or disseminated intravascular coagulation when patients with acquired deficiency are treated with human prothrombin complex. Patients given human prothrombin complex should be observed closely for signs or symptoms of disseminated intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, monitoring of signs and symptoms should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, patients with liver disease, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. The potential benefit of treatment should be weighed against the risk of complications. Balfaxar may not be suitable in patients with thrombotic or thromboembolic events in the prior 3 months, as it has not been studied in these patients. Resumption of anticoagulation should be carefully considered following administration of Balfaxar and vitamin K once the risk of thromboembolic events outweighs the risk of bleeding.

The most common adverse reactions observed in ≥ 3% subjects receiving Balfaxar were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting and catheter site related reaction.

© 2023 Octapharma USA Inc. All rights reserved.

1.5 Postmarketing Data

Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. The following adverse reactions have been reported during postmarketing use of Balfaxar (known as Octaplex) outside the US:

Adverse Reactions Reported During Post-Marketing Use of BALFAXAR

Immune system disorders
Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity reaction

Nervous system disorders
Cerebrovascular accident, headache, paresthesia, tremor

Cardiac disorders
Bradycardia, tachycardia, cardiac arrest

Vascular disorders
Thromboembolic events, circulatory collapse, hypotension, hypertension

Respiratory, thoracic and mediastinal disorders
Dyspnea, respiratory failure

Gastrointestinal disorders
Nausea

Skin and subcutaneous tissue disorders
Urticaria, rash, pruritus

General disorders and administration site conditions
Fever, chills

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at 1-866-766-4860 or FDA at 1-800-FDA1088 or www.fda.gov/medwatch.

1.6 Reimbursement Information

Summary of Medicare Coding for Balfaxar†

Code Type	Procedure Code	HCPCS Code	Revenue Code	Diagnosis Code(s)
Hospital Inpatient Setting	ICD-10-CM Procedure Code 30283B1‡	None	025X	Appropriate ICD-10-CM Diagnosis Codes
Hospital Outpatient Setting	Appropriate CPT code for Balfaxar admin procedure	J-Code J7165	0636 (with C-code) + revenue code for admin CPT	Appropriate ICD-10-CM Diagnosis Codes

*This resource provides information from a complex and evolving medical coding system. The treating physician is solely responsible for diagnosis coding and determination of the appropriate ICD-10-CM codes that describe the patient's condition and are supported by the medial record. All codes listed are for informational purposes and are not an exhaustive lot. The CPT, HCPCS, and ICD-10-CM codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT Coding). Because government and other third-party payor coding requirements change periodically, please verify current coding requirements directly with the payor being billed.
†Include additional billing codes as appropriate.
‡Infusion of 4F-PCC
4F-PCC = four-factor prothrombin complex concentrate; CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification; IU = international unit.

© 2023 Octapharma USA Inc. All rights reserved.

2.1 Product Summary

Balfaxar, which is also referred to as Octaplex outside of the United States (US), has been approved in other countries such as Austria, Brazil, Canada, Czech Republic, Finland, France, Germany, Ireland, Mexico and the United Kingdom (Octapharma 2023). Since 2003, approximately 1.2 million patients have been exposed to ~2.6 billion IUs of Balfaxar (Octaplex) worldwide[8].

Balfaxar is an FDA-approved non-activated 4F-PCC indicated for urgent warfarin reversal in adult patients the need for urgent surgery or invasive procedure. In the treatment of adult patients with need for an urgent surgery or an invasive procedure who require urgent VKA reversal. Balfaxar provides a safe and effective alternative to Kcentra. Balfaxar demonstrated hemostatic efficacy comparable to Kcentra in urgent surgery, with similar early and sustained INR reduction. Balfaxar replaces the deficient coagulation factors. Balfaxar is not associated with an increased risk of TE events, although patients receiving VKA therapy are predisposed to TE events, and both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Balfaxar in clinical trials and postmarketing surveillance.

Balfaxar provides several key advantages:

- In achieving hemostatic efficacy, Balfaxar was non-inferior to Kcentra in the urgent surgery/ invasive procedure trial
- Balfaxar achieved INR reduction to ≤1.5 at 30 minutes after the end of infusion in 78.1% of subjects vs. 71.8% in the Kcentra subjects
- Balfaxar replaces all the vitamin K–dependent coagulation factors depleted by warfarin: II, VII, IX, X as well as the antithrombotic Proteins C and S
- Balfaxar reconstitutes quickly (1 to 5 minutes) at room temperature
- The reconstituted solution can be stored 2x longer than Kcentra, 8 hours (vs 4 hours) at room temperature provided sterility is maintained
- Balfaxar is provided with the user-friendly transfer device (nextaro) for reconstitution of the lyophilized powder in diluent (sterile Water for Injection (sWFI))
- Balfaxar can be administered without the need for thawing or ABO typing
- Balfaxar can be stored at 2°C to 25°C (36°F to 77°F) for up to 36 months from the date of manufacture

2.2 Product Information

2.2.1 Indication and Usage

Balfaxar, Prothrombin Complex Concentrate (Human), is indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, eg, warfarin) therapy in adult patients with need for urgent surgery or an invasive procedure.

2.2.2 Dosage and Administration

Balfaxar is available as a single-use vial containing coagulation Factors II, VII, IX, and X and antithrombotic Proteins C and S as a lyophilized concentrate. Administer vitamin K concurrently to patients receiving Balfaxar to maintain vitamin K–dependent clotting factor levels once the effects of Balfaxar have diminished. Dosing is individualized based on the patient's pre-dose INR and body weight (kg) up to 100 kg. Repeat dosing with Balfaxar is not supported by clinical data and is not recommended.

Dosage

Balfaxar is for intravenous (IV) use after reconstitution only. Balfaxar dosing should be individualized based on the patient's baseline INR value, and body weight – see the table below. The safety and effectiveness of repeat dosing have not been established and it is not recommended.

Pre-treatment INR	Dose of Balfaxar (units of FIX)/kg body weight	Maximum dose (units of FIX)
2 ≤ 4	25	Not to exceed 2500
4 – 6	35	Not to exceed 3500
> 6	50	Not to exceed 5000

Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-32 Factor IX units/ml after reconstitution. The actual potency for a 500-unit vial ranges from 400-640 units/vial. The actual potency for a 1000unit vial ranges from 800-1280 units/vial.

For details on dosage and administration, see full prescribing information, section 2.1. Concurrent administration of vitamin K is important to maintain the INR in the normal range beyond the immediate effects of Balfaxar. Because some of the administered coagulation factors have a relatively short half-life (e.g., Factor VII), normal physiologic production of vitamin K–dependent coagulation factors is important to maintain factor levels once the effects of Balfaxar have diminished.

© 2023 Octapharma USA Inc. All rights reserved.

Administration

Balfaxar is available as a single-use vial of either 500 units or 1,000 units that contains non-activated coagulation Factors II, VII, IX, and X and antithrombotic Proteins C and S as a lyophilized concentrate for IV infusion. Balfaxar potency (units) is defined by Factor IX content. The range of Factor IX units per vial is 400 to 640 units for the 500-unit vial and 800 to 1,280 units for the 1,000-unit vial. After reconstitution at room temperature with sterile water for injection (20 mL for the 500-unit vial and 40 mL for the 1,000-unit vial), the final concentration of drug product in Factor IX units will be in a range from 20 to 32 units/mL. The actual content of Factor IX, as measured in units of potency, is stated on the vial and carton. The potency ranges of each coagulation factor (Factors II, VII, IX and X) and for antithrombotic Proteins C and S are also stated on the vial label and carton.

The composition of Balfaxar is as follows:

Component	Potency Range for 500 IU vial	Potency Range for 1000 IU vial
Human Coaqulation Factor II	340-500 IU	680-1000 IU
Human Coaqulation Factor VII	240-400 IU	480-800 IU
Human Coaqulation Factor IX	400-640 IU	800-1280 IU
Human Coaqulation Factor X	300-540 IU	600-1080 IU
Protein C	320-560 IU	640-1120 IU
Protein S	240-600 IU	480-1200 IU
Heparin	80-384 IU	160-768 IU
Sodium Citrate	16.8-23.4 mmol/L	16.8-23.4 mmol/L

Balfaxar should not be mixed with other medicinal products and should be administered through a separate infusion line. Use aseptic technique when administering Balfaxar. Administer at room temperature by intravenous (IV) infusion at a rate of 0.12 mL/kg/ minute (~3 units/kg/minute), up to a maximum rate of 8.4 mL/minute (~210 units/minute). No blood should enter the syringe as there is a possibility of fibrin clot formation. Please see full prescribing information, section 2.

2.2.3 Manufacturing Information

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. The actual potency printed on the vial label represents the potency of Factor IX. Balfaxar is sterile, endotoxin-free, and does not contain preservatives. No albumin is added as a stabilizer, and the excipients are heparin and sodium citrate. The diluent for reconstitution of the lyophilized powder is sterile Water for Injection.

All human plasma used in the manufacture of Balfaxar is obtained from U.S. 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 B19V to exclude donations with high titers. The limit for the titer of B19V DNA in the manufacturing pool is set not to exceed 10^4 IU/mL. Only plasma that passed virus screening is used for production.

The Balfaxar manufacturing process has the capability to reduce viruses by a solvent/detergent (S/D) virus inactivation step and a virus removal nanofiltration step. The mean cumulative virus reduction factors of these steps are summarized in the table below.

Virus Reduction During BALFAXAR Manufacturing

Production Step	Virus Reduction Factor [$\log^{10}$]				
	Enveloped Viruses			Non-Enveloped Viruses	
	HIV-1	BVDV	PRV	HAV	PPV
S/D treatment	≥ 4.35	≥ 5.96	≥ 5.77	n.a.	n.a.
Nanofiltration (Planova 20N or Pegasus SV4)	≥ 4.58	≥ 5.01	≥ 6.01	≥ 5.24	3.98
Global Reduction Factor	**≥ 8.93**	**≥ 10.97**	**≥ 11.78**	**≥ 5.24**	**3.98**

n.a.: not applicable
BVDV: Bovine Viral Diarrhea Virus, model for HCV
PRV: Pseudorabies Virus, model for large enveloped DNA viruses, e.g., HBV
PPV: Porcine Parvovirus, model tor B19V

© 2023 Octapharma USA Inc. All rights reserved.

2.3 Disease Description

Anticoagulation is widely used to prevent or treat conditions associated with abnormal blood clotting including but not limited to, atrial fibrillation, VTE, DVT, PE, MI, stroke, and prevention of thromboembolism in patients with prosthetic heart valves[9-12]. Although treatment with anticoagulants is critical for these conditions, there are times when reversal of anticoagulants is necessary[13,14]. Bleeding emergencies or urgent surgery and invasive procedures that increase the risk of bleeding may require the use of reversal agents such as vitamin K, FFP, or a coagulation factor replacement therapy.

The following sections focus on anticoagulation therapies and potential scenarios requiring anticoagulant reversal. Factors influencing the risk of bleeding, the underlying pathophysiology of coagulation, manifestations of bleeding, as well as the broader impact encompassing the burden of anticoagulation-associated bleeding, will be addressed.

2.3.1 Epidemiology and Relevant Risk Factors

Available oral anticoagulation agents include the VKA, warfarin, and DOACs such as rivaroxaban, apixaban, edoxaban, and dabigatran. Broadly, these agents are indicated for treatment and prevention of major cardiovascular events. Mechanistically, VKAs inhibit the synthesis of vitamin K-dependent clotting factors (II VII, IX, and X) and proteins C and S while DOACs work to directly inhibit specific factors such as thrombin or factor Xa[15].

Atrial fibrillation incidence offers an estimate of the amount of use of these oral anticoagulants in the US; atrial fibrillation affects an estimated 5.2 million individuals in the US and is projected to affect an estimated 12.1 million by 2030[16,17].

- More than 80% of patients with atrial fibrillation may require oral anticoagulation therapy[18].
- Atrial fibrillation is a leading indication for oral anticoagulation use[19].

2.3.1 Epidemiology and Relevant Risk Factors (continued)

Other estimates include VTE (ie, DVT and PE) and MI which affect approximately 1 to 2 per 1,000 person years and 3.1% of individuals in the US, respectively.[20-22] In 2006, it was estimated that 2.5 million individuals in the US were on VKA therapy and a more recent estimate of patients taking oral anticoagulants, using IMS Health National Disease and Therapeutic Index data of outpatient visits (2009–2014), showed that over 6 million individuals in the US are treated with oral anticoagulants for various indications.[23,24]

With use of oral anticoagulants comes potential risk of bleeding. In the US, data from emergency department visits (2016–2020) showed approximately 1.27 million visits were for bleeding from oral anticoagulant use, accounting for over 250,000 emergency department visits annually. Bleeds on oral anticoagulation therapy accounted for 87.0% of all AEs associated with oral anticoagulation during the study period.[25]

- The majority (80.1%) of bleeding events occurred in adults aged ≥65 years. Notably, adults aged ≥80 years exhibited the highest 5-year rate of emergency department visits, estimated at 13.1 visits per 100 recipients of oral anticoagulants. This rate was more than 3 times higher than that observed in adults aged <45 years.
- Almost half (48.0%) of the emergency department visits resulted in hospitalization.
- There were 13.0 emergency department visits per 100 patients receiving warfarin vs 5.9 for patients receiving DOACs.
- Gastrointestinal bleeding accounted for most (34.5%) of the bleeding events; similar rates for warfarin (30.1%) and DOACs (39.3%) were observed.
- Other bleeding events included skin/wound/other minor bleeding (22.4%), epistaxis (19.0%), genitourinary bleeding (11.1%), other types of hemorrhage (5.8%), central nervous system (CNS) bleeding (4.5%), and pulmonary bleeding (2.6%).

© 2023 Octapharma USA Inc. All rights reserved.

2.3.1 Epidemiology and Relevant Risk Factors (continued)

Risk Factors

Many factors influence the risk of bleeding in patients on anticoagulants. Factors associated with higher risk of bleeding include the following:[26]

- Age (≥65 years and especially ≥80 years is associated with higher rate of bleeding in recent studies;[26]
- Alcohol abuse disorder
- Comorbid conditions like cancer, renal insufficiency, liver disease, arterial hypertension, and prior stroke
- Concomitant antiplatelet medications such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Certain antibiotics such as penicillins and moxalactam.

Intensity of anticoagulant therapy is the most important factor influencing the risk of bleeding; when INR increases above 5.0, the risk of bleeding increases.

2.3.2 Pathophysiology

When bleeding or injury occurs the coagulation cascade, a series of complex interactions that lead to the formation of a blood clot, is initiated.[27,28] Initiation can occur through 2 pathways, the intrinsic system and the extrinsic system as shown in Figure 2-2 Throughout the cascade, different factors are activated and thrombin, a key enzyme in the coagulation process, is generated. Platelets are activated and thrombin acts on fibrinogen, leading to the formation of a blood clot.

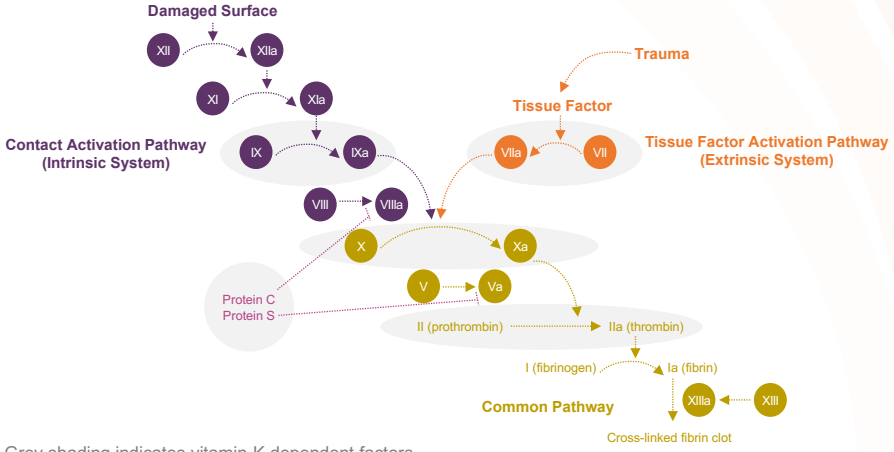
2.3.2 Pathophysiology (continued)

As described in Section 2.3.1, there are many reasons anticoagulation therapy is utilized for the prevention or management of medical conditions linked to abnormal blood clotting. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K-dependent clotting factors.

- Warfarin is thought to interfere with clotting factor synthesis (factors II, VII, IX, and X) by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide.[31]
- DOACs work by targeting and inhibiting specific coagulation proteins in the coagulation pathway.[9,15,29]

Bleeding, including spontaneous bleeding, trauma-related bleeding, and bleeding during an emergency or elective surgery is a substantial concern with the use of any anticoagulation therapy. In the event that bleeding occurs, a PCC, which works by increasing plasma levels of coagulation factors II, VII, IX and X as well as protein C and protein S to stop or prevent bleeding and help restore hemostasis, can be used.

Coagulation Cascade



Grey shading indicates vitamin-K dependent factors.

© 2023 Octapharma USA Inc. All rights reserved.

2.3.3 Clinical Presentation

Risk Factors

Warfarin, a VKA, is indicated for prophylaxis and treatment of VTE, thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, and the reduction in the risk of death in recurrent MI, and TEEs such as stroke or systemic embolization after MI.[30]

- The International Normalized Ratio (INR) is a laboratory measurement that is used to indicate hemorrhagic risk in patients taking warfarin.[24] The goal of VKA therapy is to increase INR to between 2 to 3; the risk of symptomatic thromboembolism increases when INR is below 2 and risk of bleed increases when INR surpasses 5.
- Difficulties in maintaining a stable therapeutic range with warfarin can lead to overtreatment.
- Patients on warfarin can have an increased risk of bleeding during surgery. Therefore, warfarin may be temporarily discontinued, or rapid reversal of anticoagulant effects may be needed.[6]
    - Examples of these types of invasive surgery requiring warfarin reversal include cardiothoracic, neuro, and orthopedic surgeries.

2.3.4 Disease Burden

Using data from the Randomized Evaluation of Long-Term Anticoagulation (RE-LY) trial, it was found that in patients receiving VKA therapy, periprocedural bleeding occurred in 3.3% of elective procedures and 21.6% of emergency procedures.[31]

To help reduce perioperative bleeding for urgent surgery/invasive procedure, guidelines recommend rapid warfarin reversal and replacement of vitamin K dependent coagulation factors.[26]

The aging population is leading to more patients receiving long-term anticoagulation and at risk of surgical complications if anticoagulant effects are not reversed.[6,16]

© 2023 Octapharma USA Inc. All rights reserved.

2.4 Approaches to Treatment

In cases of urgent procedures, emergency reversal in a critical care setting is often necessary for patients on oral anticoagulants. For rapid reversal of VKAs, guidelines recommend the use of (4F-PCC) and vitamin K.[5-7] Guidelines prefer 4F-PCC to FFP and over 3F-PCC.

Reversal agents for anticoagulation include 4F-PCC and FFP; other products used include 3F-PCC, recombinant factor VIIa (rFVIIa) and vitamin K.[32] The effectiveness of reversal agents are assessed by monitoring INR to determine clotting time.

Vitamin K

Vitamin K serves as a targeted reversal agent for VKA therapy by reinstating the intrinsic hepatic carboxylation process of vitamin K-dependent clotting factors.[24] In doing so, it counteracts the effects of VKA by overcoming its inhibitory actions.

- Prompt administration of vitamin K does not immediately correct anticoagulation, therefore, during a major bleed repletion is necessary with PCCs or FFP, if PCCs are not available.

Fresh frozen plasma (FFP)

FFP is considered a nonspecific reversal agent; along with vitamin K dependent clotting factors, FFP contains other coagulation factors and proteins. Randomized studies have demonstrated that FFPs exhibit a similar safety profile to 4F-PCCs, however, they are associated with greater fluid overload events.[33]

- When utilizing FFP for VKA reversal, many considerations are necessary.[24,30] Plasma transfusion necessitates ABO blood type matching and thawing of frozen plasma, resulting in a potential delay of up to 90 minutes from the order to the administration of the first unit.
- Adequate dosing for VKA reversal requires 15-30 mL/kg of plasma as 1 unit of factor is present in 1 mL of normal pooled plasma however practical dosing is 10-15 mL/kg. Prolonged infusion times and large volumes are evident with VKA reversal using FFP.
- Approximately 20% of individuals who receive FFP for warfarin reversal develop pulmonary complications such as transfusion-related lung injury.[32,34]

Prothrombin complex concentrates (PCCs)

PCCs are composed of purified vitamin K-dependent clotting factors that are derived from human plasma. 4F-PCCs contain FII, FVII, FIX, FX, and protein C and S.[24] Concentrations of coagulation factors in 4F-PCCs can be up to 25 times higher than those found in plasma obtained from healthy donors .[35,36]

- The total volume of fluid needed for reversing coagulopathy induced by VKAs is reduced when using 4F-PCCs compared to FFP. This lower fluid volume theoretically decreases the risk of fluid overload and allows for faster administration of the necessary dose.
- 4F-PCCs can be conveniently stored as a lyophilized powder at room temperature; consequently, they can be promptly reconstituted and administered via infusion. ABO compatibility is not required.
- In LEX-209, Balfaxar and Kcentra were compared in a non-inferiority, urgent surgery / invasive procedure study.[1,42] The treatment-related TEE rates in both groups were similar (1% vs 0%, respectively). Refer to Section 3.0.
- In a surgery study of 4F-PCC vs FFP, both AEs (60.2% vs 62.9%) and SAEs (28.3% vs 24.9%) had comparable rates for 4F-PCC and FFP, respectively.[49] The percentage of patients experiencing TEEs was comparable in both groups, with 7.3% (14/191) in the 4F-PCC group and 7.1% (14/197) in the FFP group. In terms of mortality, both the 4F-PCC and the FFP group had a similar rate of deaths, with 6.8% (13 cases) and 6.6% (13 cases), respectively. However, fluid overload events were more prevalent in the FFP group, affecting 12.7% (25 cases) of patients compared to 4.7% (9 cases) in the 4F-PCC group.

The American College of Cardiology (ACC) Expert Consensus Decision Pathway on the Management of Bleeding in Patients on Oral Anticoagulants recommends the use of four-factor prothrombin complex concentrates (4F-PCCs) for reversal for patients taking warfarin or other VKAs.[24]

© 2023 Octapharma USA Inc. All rights reserved.

2.5 Benefits of Balfaxar

2.5.1 Clinical Benefits

2.5.1.1 Key Efficacy Findings

A phase 3, prospective, randomized, double-blind, multicenter, non-inferiority study comparing two four-factor prothrombin complex concentrates for reversal of vitamin K antagonist-induced anticoagulation in adult patients needing urgent surgery with significant bleeding risk. *Blood.* 2022;140(Supplement 1):352-353. Clinicaltrials.gov ID: NCT02740335.[42]

Objective: Compare the hemostatic efficacy of Balfaxar with an active control (Kcentra) for urgent surgery in those on VKA for anticoagulation.

Study dates: June 2017 to November 2021 (note: trial stopped early; primary endpoint met at interim analysis)

Trial design: Prospective, randomized, open-label, active-controlled, non-inferiority, multicenter, phase 3 trial.

Key inclusion/exclusion criteria:

Inclusion: Adults aged ≥18 years, currently anticoagulated with coumadin or warfarin with an INR ≥2, requiring urgent surgery with a significant risk for bleeding where VKA withdrawal or oral/parenteral vitamin K is inappropriate.

Exclusion: Patient life expectancy <48 hours; low bleeding risk procedures or procedures with unknown expected blood loss; history of TEE; history of other cardiovascular events such as MI, unstable angina pectoris, critical aortic stenosis, cerebrovascular accident, TIA, severe peripheral vascular disease, DIC within 3 months, thrombocytopenia <80,000/µL or history of HIT; those that have received >5,000 units of unfractionated heparin, any dose of non-VKA anticoagulation within 24 hours, or had potential to receive these before completion of hemostasis evaluation at the end of surgery; those that have received PCCs, FFP, or vitamin K within 72 hours; and those on P2Y12 platelet inhibitors.

2.5.1.1 Key Efficacy Findings (continued)

Treatment: Patients received either Balfaxar (n=105) or Kcentra (n=103) using weight- and INR-based dosing for a single IV dose as follows:

- 25 IU/kg for INR 2–<4
- 35 IU/kg for INR 4–6
- 50 IU/kg for INR >6

Patient characteristics: A total of 208 patients were enrolled. Refer to the table below for key characteristics.

Demographic and baseline characteristics

Characteristic	Balfaxar (n=105)	Kcentra (n=103)
Age, median, years (IQR)	67 (31-90)	68 (32-92)
Female, n (%)	47(44.8)	43(41.7)
Estimated maximum blood loss ≥ 2200ml, n (%)	71 (67.6)	69 (67.0)
Baseline INR, median (IQR)	3.0 (2.4-4.0)	3.0 (2.4-4.1)
Median dose, IU/kg (IQR)	25(16-50)	25 (15-50)

Key: INR - international normalized ratio; IQR - interquartile ratio.

Clinical outcomes:

Primary effectiveness endpoint: Non-inferiority of Balfaxar compared to Kcentra
In the final analysis, effective hemostasis was achieved in 94.3% vs 94.2% of patients receiving Balfaxar vs Kcentra, respectively (95% CI: 0.080, 0.082; P<0.001).

Primary endpoint

Hemostatic Efficacy Rating[a]	Balfaxar (%) (n=105)	Kcentra (%) (n=103)
Effective[b]	99 (94.3)	97 (94.2)
Ineffective	6 (5.7)	6 (5.8)

[a] Ratings of excellent and good were considered to be effective hemostasis, whereas ratings of moderate and none were considered to be ineffective hemostasis. Imputation for ineffective was performed for missing rating or additional coagulation therapy after initial investigational medicinal product infusion as none.

[b] Ratings of 'Excellent' or 'Good' considered effective hemostasis.

© 2023 Octapharma USA Inc. All rights reserved.

2.5.1.1 Key Efficacy Findings (continued)

Secondary effectiveness endpoints

- INR reduction to ≤1.5 at 30 minutes post infusion: 78.1% in Balfaxar vs 71.8% in Kcentra (proportion difference: 0.063; 95% CI: 0.056, 0.181) – see table below.
- Plasma levels of FII, FVII, FIX, FX, and protein C and protein S: similar between groups.

Decrease of INR (to 1.5 or Less at 30 Minutes after End of Infusion) in Urgent Surgery RCT

Rating	No. (%) of subjects		Proportion difference BALFAXAR vs Kcentra (95% CI for difference)
	Balfaxar (N=105)	Kcentra (N=103)	
Decrease of INR to ≤ 1.5 at 30 min	82 (78.1)	74 (71.8)	6.3% (-5.5%, 18.0%)

2.5.1.2 Safety outcomes:

Safety was assessed at Days 3, 21, and 45 post-surgery. TEAEs (81.9% and 77.7%) and drug-related TEAEs (1.0% and 1.0%) were similar between Balfaxar and Kcentra, respectively.

The most common adverse reactions observed in ≥3% of subjects were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting, and catheter site related reaction. The number of thromboembolic adverse reactions assessed as at least possibly related to study treatment was one (1%) with Balfaxar (unstable angina) vs 0% in the control group.

The following table provides clinical evidence to support Balfaxar for use in VKA reversal for surgery.

Citation (Country)	Trial design and treatments	Sample-size, trial duration and follow-up	Key inclusion/ exclusion criteria	Efficacy and safety results
VKA reversal in surgery				
LEX-209 BALFAXAR prescribing information. Octapharma USA,Inc. July 2023. Sarode R, Goldstein J, Simonian G, et al. *JAMA Network Open.* 2024;7(8):e2424758. doi:10.1001/jamanetworkopen.2024.24758 (US)	*Design:* Phase 3, prospective, randomized, open-label, active-controlled, non-inferiority, multicenter study *Treatment:* Balfaxar/ Octaplex or Kcentra • 25 IU/kg for INR 2-<4 • 35 IU/kg for INR 4-6 • 50 IU/kg for INR >6	N= 208 • Balfaxar/ Octaplex, n=105 • Kcentra, n=103 *Duration of data collection:* June 2017 – November 2021; note: trial stopped early; primary endpoint met at interim analysis *Follow-up:* 45 days post-surgery	*Inclusion:* • Adults ≥ 18 years • VKA therapy • Hospitalized for urgent surgery with a significant risk for bleeding (≥ 50 mL expected blood loss in patients with normal hemostasis) where VKA withdrawal or vitamin K is insufficient • Had surgery initiated within 24 hours after the start of 4F-PCC infusion (within 5 hours for the per-protocol population) • INR ≥ 2.0 Exclusion: • History of TEEs • Life expectancy < 48 hours • History of cardiac events • DIC within 3 months • Thrombo-cytopenia • History of HIT • Previous heparin usage • Prior blood thinners within 72 hours of inclusion	*Primary endpoint:* Hemostatic Efficacy Rating[a] / Balfaxar/ Octaplex (%) (n=105) / Kcentra (%) (n=103) Effective: 99 (94.3) / 97 (94.2) Ineffective: 6 (5.7) / 6 (5.8) [a] Ratings of excellent and good were considered to be effective hemostasis, whereas ratings of moderate and none were considered to be ineffective hemostasis. Imputation for ineffective was performed for missing rating or additional coagulation therapy after initial investigational medicinal product infusion as none. *Secondary endpoints:* • INR reduction to ≤1.5 at 30 minutes post infusion: 78.1% vs 71.8% for Balfaxar/ Octaplex vs Kcentra, respectively; proportion difference: 0.063; 95% CI: 0.056, 0.181 • Plasma levels of FII, FVII, FIX, FX, and protein C and protein S: similar between groups *Safety:* • TEAEs: 81.9% and 77.7% for Balfaxar/Octaplex and Kcentra, respectively • Drug-related TEAEs: 1.0% for both groups • Treatment-related TEEs: Balfaxar/Octaplex, 1% (unstable angina possibly related); Kcentra, 0%

© 2023 Octapharma USA Inc. All rights reserved.

2.5.1.3 Key Product Features – nextaro

- A user preference study was conducted to assess the usability of the nextaro device for the transfer of reconstitution fluid, designed as an alternative to the established Mix2Vial® device for facilitating the mixing process for users.[38] Octapharma collaborated with smf medical devices GmbH to design the nextaro device with the intention of providing an improved user experience (https://www.nextaro.com/en/#the-product). Octapharma utilizes the nextaro transfer device, while Kcentra uses the Mix2Vial device.

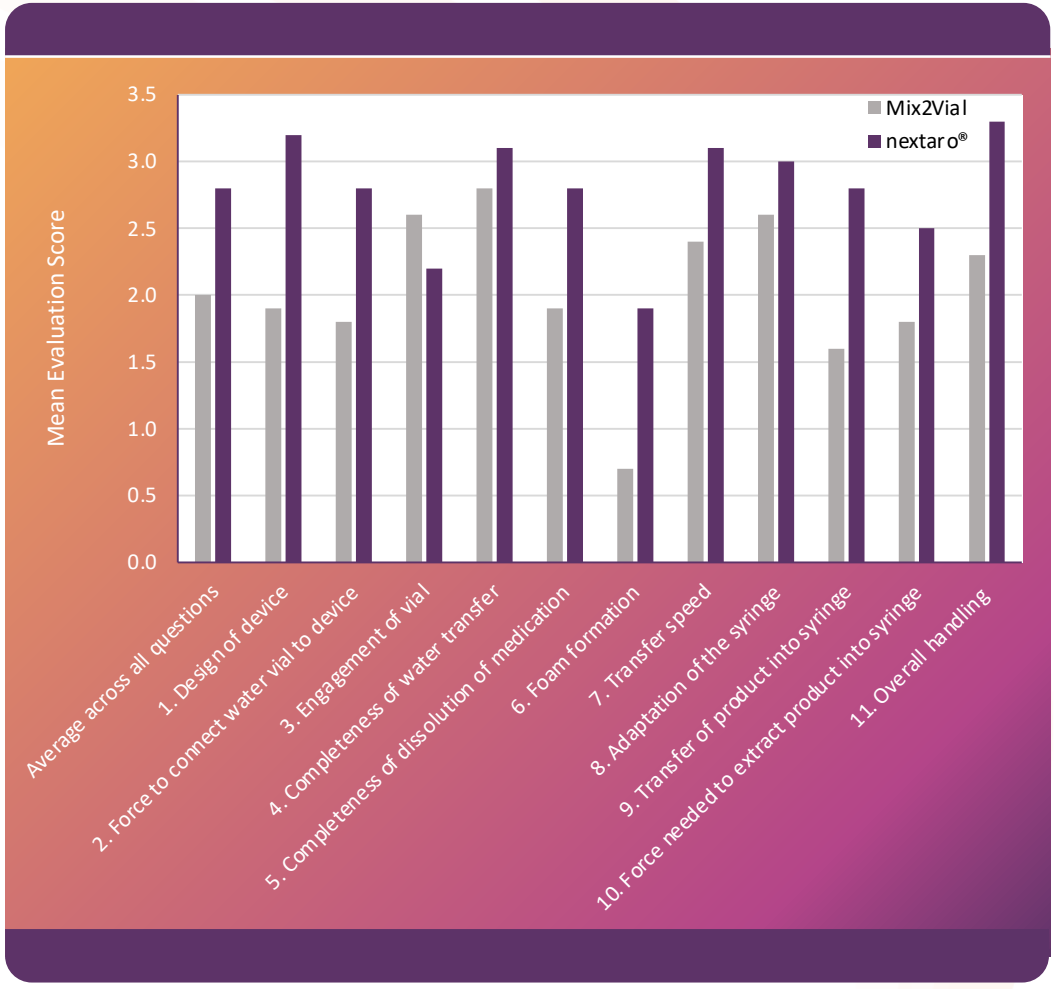
- The usability study enrolled 16 healthcare professionals, the majority of whom were nurses (43.8%) or physicians (37.5%), to perform a series of reconstitution trial runs with each device. After each trial run, participants completed an 11-item questionnaire to assess device usability. Notably, the order of device testing varied across the three sessions, and all the trial runs were for testing purposes only (ie, no patients received product).

- The 11 questions in the questionnaire were rated on a scale of -4 (negative) to +4 (positive) with higher scores indicating greater satisfaction/more positive experience. Data were descriptive only. Descriptive data revealed positive mean values (>0) for the primary variable, the average score across all questions, as well as for each individual questions for both devices. The average mean score across all 11 questions showed preference for the nextaro transfer device (mean: 2.8) compared to the Mix2Vial transfer device (mean: 2.0). With the exception of 1 question regarding the completed and audible engagement of the vial, all participants favored nextaro over the Mix2Vial device (See Figure 2 1).

- The largest absolute differences in means in favor of nextaro were observed for the design of the device, slightness of foam formation, and the transfer of the reconstituted product into the syringe. Results from this user preference study indicate that healthcare professionals in the clinical setting preferred the optimized nextaro transfer device over the Mix2Vial device.

Mix2Vial is a registered trademark of West Pharmaceutical Services

Nextaro® vs Mix2Vial User Preference Study Evaluation Scores



© 2023 Octapharma USA Inc. All rights reserved.

3 | *Production Comparison Table*

Urgent Reversal of Acquired Coagulation Factor Deficiency Induced by VKA Therapy

	Balfaxar® (prothrombin complex concentrate (human))	KCENTRA® (prothrombin complex concentrate (human))
Package insert	Updated: July 2023	Updated: May 2023
Manufacturer	Octapharma USA, Inc.	CSL Behring
Indications for use	Blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA (eg, warfarin) therapy in adult patients with need for urgent surgery/invasive procedure.	Blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA (eg, warfarin) therapy in adult patients with acute major bleeding or need for an urgent surgery/invasive procedure.
Dosage forms and strengths	White to ice-blue lyophilized powder for reconstitution for IV use in a single-dose vial, provided in a nominal strength of 500 FIX units in 20 mL reconstitution volume and 1000 FIX units in 40 mL reconstitution volume per vial. Balfaxar contains the coagulation FII, FVII, FIX, and FX and antithrombotic Proteins C and S.	White or slightly colored lyophilized concentrate in a single-dose vial containing coagulation FII, FVII, FIX and FX, and antithrombotic Proteins C and S.
Storage	• Balfaxar is supplied in a package with a single-dose vial of lyophilized powder and a vial of diluent (sWFI), together with a transfer device. • Components used in the packaging of Balfaxar are not made with natural rubber latex. • Store Balfaxar for up to 36 months at 2°C to 25°C (36°F to 77°F) from the date of manufacture. Do not freeze. • Do not use beyond the expiration date on the vial label and carton. • Store the vial in the original package to protect it from light.	• KCENTRA is supplied in a single-dose vial. • The KCENTRA packaging components are not made with natural rubber latex. Prior to reconstitution: • Store KCENTRA between 2-25°C (36-77°F), this includes room temperature, not to exceed 25°C (77°F). Do not freeze. • KCENTRA is stable for 36 months from the date of manufacture, up to the expiration date on the carton and vial labels. • Do not use KCENTRA beyond the expiration date on the vial label and carton. • Store the vial in the original carton to protect it from light.

	Balfaxar® (prothrombin complex concentrate (human))	KCENTRA® (prothrombin complex concentrate (human))
Transfer device	nextaro® (https://www.nextaro.com/en/#the-product)	Mix2Vial (https://adelphi-hp.com/product-range/mix2vial)
Transfer device features	• Maximum protection from contamination through 2 filters • The optimized haptics handling • Sturdy and robust threaded design prevents overtwisting • Adaption for water vial marked with drop shapes 	• Vacuum-activated • Easy to use • Rapid transfer • No repeat piercing • Molded from medical-grade polycarbonate
Reconstitution	Reconstitute the Balfaxar powder only directly before use. Use the solution immediately after reconstitution. However, if it is not administered immediately, the reconstituted solution can be stored for up to 8 hours at room temperature (20°C to 25°C; 68°F to 77°F), provided sterility of the stored product is maintained. Discard partially used vials. Balfaxar is provided with a transfer device (nextaro®) for reconstitution of the lyophilized powder in diluent sWFI.	KCENTRA must be used within 4 hours following reconstitution. Reconstituted KCENTRA can be stored at 2-25°C. If cooled, the solution should be warmed to 20-25°C prior to administration. Do not freeze. Discard partially used vials.
Dosage and administration	For IV use after reconstitution only.	For IV use after reconstitution only.

© 2023 Octapharma USA Inc. All rights reserved.

Urgent Reversal of Acquired Coagulation Factor Deficiency Induced by VKA Therapy

	Balfaxar® (prothrombin complex concentrate (human))	KCENTRA® (prothrombin complex concentrate (human))
Transfer device features	Balfaxar dosing should be individualized based on the patient's baseline INR value, and body weight. Administer Vitamin K concurrently to patients receiving Balfaxar to maintain factor levels once the effects of Balfaxar have diminished. The safety and effectiveness of repeat dosing have not been established and it is not recommended. Administer reconstituted Balfaxar 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). **Pre-treatment INR / Dose[a] of BALFAXAR (units[b] of FIX)/kg body weight / Maximum dose[c] (units of FIX)** 2 ≤ 4 / 25 / Not to exceed 2500 4 – 6 / 35 / Not to exceed 3500 > 6 / 50 / Not to exceed 5000 [a] Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-31 Factor IX units/mL after reconstitution. The actual potency for a 500 unit vial ranges from 400-620 units/vial. The actual potency for a 1000 unit vial ranges from 800-1240 units/vial. b Units refer to International Units. [c] Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.	KCENTRA dosing should be individualized based on the patient's baseline INR value, and body weight. Administer Vitamin K concurrently to patients receiving KCENTRA to maintain factor levels once the effects of KCENTRA have diminished. The safety and effectiveness of repeat dosing have not been established and it is not recommended. Administer reconstituted KCENTRA 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). **Pre-treatment INR / Dose[a] of KCENTRA (units[b] of FIX)/kg body weight / Maximum dose[c] (units of FIX)** 2 ≤ 4 / 25 / Not to exceed 2500 4 – 6 / 35 / Not to exceed 3500 > 6 / 50 / Not to exceed 5000 [a] Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-31 Factor IX units/mL after reconstitution. The actual potency for a 500 unit vial ranges from 400-620 units/vial. The actual potency for a 1000 unit vial ranges from 800-1240 units/vial. b Units refer to International units. [c] Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.
Mechanism of action	The administration of Balfaxar provides a rapid increase in plasma levels of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX) and antithrombotic proteins C and S. Together they are referred to/known as the prothrombin complex. Balfaxar can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.	KCENTRA contains the Vitamin K-dependent coagulation FII, FVII, FIX, and FX, together known as the Prothrombin Complex, and the antithrombotic Protein C and Protein S.

	Balfaxar® (prothrombin complex concentrate (human))	KCENTRA® (prothrombin complex concentrate (human))
Mechanism of action		A dose-dependent acquired deficiency of the Vitamin K-dependent coagulation factors occurs during VKA treatment. VKA exert anticoagulant effects by blocking carboxylation of glutamic acid residues of the Vitamin K-dependent coagulation factors during hepatic synthesis, lowering both factor synthesis and function. The administration of KCENTRA rapidly increases plasma levels of the Vitamin K-dependent coagulation FII, FVII, FIX, and FX as well as the antithrombotic Proteins C and S.
Contra-indications	Known anaphylactic or severe systemic reactions to Balfaxar or any of the components of the product. For a complete listing of ingredients. Known allergy to heparin or history of HIT. IgA deficient patients with known antibodies against IgA.	Known anaphylactic or severe systemic reactions to KCENTRA or any components in KCENTRA including heparin, FII, FVII, FIX, FX, Proteins C and S, Antithrombin III and human albumin. Disseminated intravascular coagulation. Known HIT. KCENTRA contains heparin.
Boxed warnings	**Arterial and Venous Thromboembolic Complications** Patients being treated with VKA therapy have underlying disease states that predispose them to TEEs. Potential benefits of reversing VKA should be weighed against the potential risks of TEEs, especially in patients with the history of a TEE. Resumption of anticoagulation should be carefully considered as soon as the risk of TEEs outweighs the risk of acute bleeding.	**Arterial and Venous Thromboembolic Complications** Patients being treated with VKA therapy have underlying disease states that predispose them to TEEs. Potential benefits of reversing VKA should be weighed against the potential risks of TEEs, especially in patients with the history of a TEE. Resumption of anticoagulation should be carefully considered as soon as the risk of TEEs outweighs the risk of acute bleeding.

© 2023 Octapharma USA Inc. All rights reserved.

3 | Production Comparison Table

Urgent Reversal of Acquired Coagulation Factor Deficiency Induced by VKA Therapy

	Balfaxar® (prothrombin complex concentrate (human))	KCENTRA® (prothrombin complex concentrate (human))
Boxed warnings	***Arterial and Venous Thromboembolic Complications*** • Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Balfaxar in clinical trials and post marketing surveillance. Monitor patients receiving Balfaxar for signs and symptoms of TEEs. • Balfaxar may not be suitable in patients with TEEs in the prior 3 months.	***Arterial and Venous Thromboembolic Complications*** • Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with KCENTRA in clinical trials and post marketing surveillance. Monitor patients receiving KCENTRA for signs and symptoms of TEEs. • KCENTRA was not studied in subjects who had a TEE, MI, disseminated intravascular coagulation, cerebral vascular accident, TIA, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. KCENTRA may not be suitable in patients with TEEs in the prior 3 months.
Warnings and precautions	Discontinue infusion if allergic or anaphylactic-type reactions occur. Initiate appropriate treatment. Arterial and venous thromboembolic complications have been reported in patients receiving Balfaxar. Monitor patients receiving Balfaxar for signs and symptoms of TEEs. Balfaxar is made from human plasma; therefore, may carry the risk of transmitting infectious agents, eg, viruses, the vCJD agent, and theoretically, the CJD agent.	Hypersensitivity reactions may occur. If necessary, discontinue administration and institute appropriate treatment. Arterial and venous thromboembolic complications have been reported in patients receiving KCENTRA. Monitor patients receiving KCENTRA for signs and symptoms of TEEs. KCENTRA was not studied in subjects who had a thrombotic or thromboembolic event within the prior 3 months. KCENTRA may not be suitable in patients with TEEs in the prior 3 months. KCENTRA is made from human blood and may carry a risk of transmitting infectious agents, eg, viruses, the vCJD agent, and theoretically, the CJD agent.
Adverse reactions	The most common adverse reactions observed in ≥3% of subjects were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting and catheter site related reaction.	Most common (≥2.8%): headache, nausea/vomiting, hypotension, and anemia. Most serious: TEEs including stroke, PE, and DVTs.

4 | Additional Clinical Studies

4.1 LEX-202: Non-randomized, non-controlled, open-label study

A total of 20 patients with study entry INRs >5.0 (active bleeding)* or >3.0 (undergoing an invasive procedure) were enrolled; half received Balfaxar for major bleeding and half for surgical interventions. The primary effectiveness endpoint was the partial thromboplastin time (PTT) reduction. Secondary effectiveness endpoints included INR reduction within 10 minutes, efficacy response rated by study physicians, and recovery of coagulation factors and protein C and S; safety endpoints included the change in vital signs.[39]

4.2 LEX-203: Non-randomized, non-controlled, open-label study

This study included adult patients treated with VKA who required PCC to prevent or control bleeding during an invasive procedure or emergency operation. The Balfaxar dose was chosen based on each patient's baseline prothrombin time (PT), which was obtained within 4 hours prior to the administration of Balfaxar. The 3 analyzed patient populations included the safety population (N=60), which consisted of patients who received Balfaxar, the full-set population (n=59), which included patients with ≥1 post-infusion PT measurement available, and the per protocol population (PPP) (n=56), which consisted of patients who fulfilled all the eligibility criteria of the study. The primary effectiveness endpoint was the first 3 measurements of post-treatment INR calculated as the geometric mean. Secondary effectiveness endpoints comprised the recovery of coagulation factors and protein C, the efficacy response rated by study physicians, and thrombin time and fibrinogen change. Safety endpoints included adverse events (AEs) and thrombogenicity markers.[40]

4.3 LEX-204: Observational study

A total of 101 patients with acquired deficiency coagulation factors experiencing acute bleeding or requiring prophylaxis due to the need for an urgent surgery or invasive procedure, received Balfaxar dosed by INR and weight. The primary effectiveness endpoint was perioperative prophylaxis of bleeding or successful treatment of acute bleeding according to clinical signs. The secondary effectiveness endpoint was the mean INR decrease.[41]

*Balfaxar is not approved for acute major bleeding

Key: CJD – Creutzfeldt-Jakob disease; DVT – deep vein thrombosis; FII – factor 2; FVII – factor 7; FIX – factor IX; FX – factor X; FVa – activated factor V; FXa – activated factor X; HIT – heparin-induced thrombocytopenia; INR – international normalized ratio; IV – intravenous; MI – myocardial infarction; PE – pulmonary embolism; sWFI – sterile Water for Injection; TEE – thromboembolic event; TIA – transient ischemic attack; vCJD – variant Creutzfeldt-Jakob disease; VKA – vitamin K antagonist.

© 2023 Octapharma USA Inc. All rights reserved.

Balfaxar demonstrates rapid and effective INR reduction across diverse studies.
Across 3 studies (LEX-202 and LEX-204), Balfaxar demonstrated a rapid reduction in INR levels. In LEX-202, INR levels dropped from an average of 6.1 ± 2 to 1.5 ± 0.3 within 10 minutes after infusion.[39] Similarly, in LEX-204, the average INR reduction observed was from 2.3 to 1.5.[41]

The efficacy response as rated by study physicians is favorable in patients who need Balfaxar
The data collected from the LEX-202, LEX-203 and LEX-204 studies consistently indicated favorable responses from treating physicians regarding Balfaxar. In LEX-202, 85% rating the efficacy response as 'good'.[39] In LEX-203, efficacy among all 5 non-responders was rated as 'excellent'.[40] Additionally, in LEX-204, efficacy in 84.2% of cases was rated as 'very good'.[41] These findings collectively underscore the positive impact of Balfaxar in clinical practice.

Balfaxar has a rapid & effective response in increasing coagulation factors and proteins C & S
The results from the LEX-203 study demonstrated rapid increases in coagulation factors (FII, FX, FVII, FIX) and protein C within 10 minutes of Balfaxar infusion, with most factors remaining stable for 4 to 6 hours post-infusion.[40] In the LEX-202 study, no significant difference in factor recoveries was observed between patients experiencing bleeding and those undergoing surgery, with protein C and S showing similar magnitudes of recovery.[39] These studies demonstrate Balfaxar's rapid and effective response in increasing coagulation factors and protein C, supporting its reliability for urgent surgical scenarios. The consistent recoveries and dose-dependent efficacy further emphasize its potential as a promising therapeutic option for VKA-induced coagulation deficiency in clinical practice.

Balfaxar exhibits favorable tolerability across various studies and applications.
The safety profile of Balfaxar is consistently favorable across studies. In LEX-203, out of the 60 AEs reported during the trial, only 3 were considered possibly related to Balfaxar infusion.[40] Furthermore, LEX-202 demonstrated that the administration of Balfaxar was well tolerated without any recorded changes in vital signs during or after the procedure.[39] LEX-204 revealed no instances of adverse drug reaction.[41]

Balfaxar is a globally established bleeding reversal agent.
Balfaxar has been approved in countries outside of the US (as Octaplex) since 2003. Worldwide, approximately 1.2 million patients have been exposed to ~2.6 billion IUs of Balfaxar since its initial approval.[38]

© 2023 Octapharma USA Inc. All rights reserved.

5 | Conclusion

Place in Therapy for Balfaxar

Guidelines recommend the use of 4F-PCCs such as Balfaxar in the event of VKA reversal. Although newly approved in the US, Balfaxar is a globally established agent used in countries such as Austria, Brazil, Canada, Czech Republic, Finland, France, Germany, Ireland, Mexico and Latin America, Norway, Portugal, Russia, Sweden, Switzerland, and the United Kingdom.[50] In a phase 3 randomized, open-label, active-controlled, non-inferiority, multicenter trial, Balfaxar was found to be non-inferior to Kcentra for VKA reversal in patients undergoing urgent surgery. Study results clinically align Balfaxar with the current treatment of choice in the US for warfarin reversal.[1]

- The balanced restoration of the prothrombin complex coagulation factors by Balfaxar is specifically designed to quickly achieve hemostasis with a similar safety profile and INR reduction time as compared to Kcentra, acting within 30 minutes.
- Additionally, unique to Balfaxar is the nextaro mixing device; technology that is convenient and user-friendly for quick preparation.[1]

In summary, Balfaxar demonstrated non-inferior hemostatic efficacy compared to the current standard of care, 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 or an invasive procedure. The user-friendly transfer device (nextaro) and Balfaxar's extended 8-hour shelf-life post-reconstitution, compared to Kcentra's 4 hours solidify Balfaxar as a promising therapeutic option as a blood coagulation factor replacement treatment.

6 | Postmarketing Study

A prospective, observational, cohort study will be conducted using electronic medical records (EMR) linked with administrative claims data, to assess occurrence of thromboembolic events after administration of Balfaxar.

7 | Reimbursement Information

A CMS ICD-10-CM procedure code exists to report the administration of Balfaxar:

Code Type	Procedure Code	HCPCS Code	Revenue Code	Diagnosis Code(s)
Hospital Inpatient Setting	ICD-10-CM Procedure Code 30283B1‡	None	025X	Appropriate ICD-10-CM Diagnosis Codes
Hospital Outpatient Setting	Appropriate CPT code for Balfaxar admin procedure	J-Code J7165	0636 (with C-code) + revenue code for admin CPT	Appropriate ICD-10-CM Diagnosis Codes

*This resource provides information from a complex and evolving medical coding system. The treating physician is solely responsible for diagnosis coding and determination of the appropriate ICD-10-CM codes that describe the patient's condition and are supported by the medial record. All codes listed are for informational purposes and are not an exhaustive lot. The CPT, HCPCS, and ICD-10-CM codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT Coding). Because government and other third-party payor coding requirements change periodically, please verify current coding requirements directly with the payor being billed.
†Include additional billing codes as appropriate.
‡Infusion of 4F-PCC
4F-PCC = four-factor prothrombin complex concentrate; CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification; IU = international unit.

© 2023 Octapharma USA Inc. All rights reserved.

8 | Contact & Ordering Information

Visit balfaxar.com
to request more information

To order BALFAXAR, use NDC Number

68982-261-01
500 IU Range FIX in 20mL
68982-261-02
1000 IU Range FIX in 40 mL

Contact Us

Octapharma USA, Inc. Corporate Office
117 W. Century Road, Paramus, NJ 07652
Ph: 201-604-1130
octapharma.com

Customer Service
Ph: 866-766-4860
uscustomerservice@octapharma.com

Medical Affairs
usmedicalaffairs@octapharma.com

Reimbursement Support
Ph: 800-554-4440

Local Octapharma Representative
Ph: 201-604-1130

For all inquiries relating to drug safety, or to report adverse events, please contact our Local Drug Safety Officer
Ph: 201-604-1137
Cell: 201-772-4546
Fax: 201-604-1141

Or contact the FDA
Ph: 1-800-FDA-1088
fda.gov/medwatch

9 | Important Safety Information

Balfaxar (prothrombin complex concentrate, human-lans) 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.

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS
Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding. Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Balfaxar in clinical trials and post marketing surveillance. Monitor patients receiving Balfaxar for signs and symptoms of thromboembolic events. Balfaxar may not be suitable in patients with thromboembolic events in the prior 3 months.

Balfaxar is contraindicated in patients with known anaphylactic or severe systemic reactions to Balfaxar or any of its components. Balfaxar is also contraindicated in patients with a known allergy to heparin, a history of heparin-induced thrombocytopenia (HIT), and IgA deficient patients with known antibodies against IgA.

In clinical trials, the most frequent (≥3%) adverse reactions observed in subjects receiving Balfaxar were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting, and catheter-site-related reaction.

Balfaxar is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

Please see full prescribing information for Balfaxar, including boxed warning starting on page 44

© 2023 Octapharma USA Inc. All rights reserved.

Appendix A | Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BALFAXAR safely and effectively. See full prescribing information for BALFAXAR.

BALFAXAR (prothrombin complex concentrate, human-lans) lyophilized powder for solution, for intravenous use
Initial U.S. Approval: 2023

WARNING: ARTERIAL and VENOUS THROMBOEMBOLIC COMPLICATIONS
See full prescribing information for complete boxed warning.

Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.

- **Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with BALFAXAR in clinical trials and post marketing surveillance. Monitor patients receiving BALFAXAR for signs and symptoms of thromboembolic events. (5.2)**
- **BALFAXAR may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)**

----------INDICATIONS AND USAGE----------
BALFAXAR (prothrombin complex concentrate, human-lans) 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. (1)

----------DOSAGE AND ADMINISTRATION----------
For intravenous use after reconstitution only.

- BALFAXAR dosing should be individualized based on the patient's baseline International Normalized Ratio (INR) value, and body weight. (2.1)
- Administer Vitamin K concurrently to patients receiving BALFAXAR to maintain factor levels once the effects of BALFAXAR have diminished. (14)
- The safety and effectiveness of repeat dosing have not been established and it is not recommended. (2.1)
- Administer reconstituted BALFAXAR 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). (2.3)

Pre-treatment INR	2-< 4	4-6	> 6
Dose# of BALFAXAR (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-32 Factor IX units/mL after reconstitution.

The actual potency for a 500 unit vial ranges from 400-640 units/vial. The actual potency for a 1000 unit vial ranges from 800-1280 units/vial.

† Units refer to International Units.

‡ Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
BALFAXAR is available as a white to ice-blue lyophilized powder for reconstitution for intravenous use in a single-dose vial, provided in 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. (3)

----------CONTRAINDICATIONS----------

- Known anaphylactic or severe systemic reactions to BALFAXAR or any of the components of the product. (4)
- Known allergy to heparin or history of heparin-induced thrombocytopenia (HIT). (4)
- IgA deficient patients with known antibodies against IgA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Discontinue infusion if allergic or anaphylactic-type reactions occur. Initiate appropriate treatment. (5.1)
- Arterial and venous thromboembolic complications have been reported in patients receiving BALFAXAR. Monitor patients receiving BALFAXAR for signs and symptoms of thromboembolic events. (5.2)
- BALFAXAR is made from human plasma; therefore, may carry the risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions observed in ≥ 3% of subjects were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting and catheter site related reaction. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at 1-866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ARTERIAL and VENOUS THROMBOEMBOLIC COMPLICATIONS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage
2.2 Preparation and Reconstitution
2.3 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
5.2 Thromboembolic Risk/Complications
5.3 Transmissible Infectious Agents
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Balfaxar®
Prothrombin Complex Concentrate, Human-lans

© 2023 Octapharma USA Inc. All rights reserved.

WARNING: ARTERIAL and VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonist (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.

- **Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with BALFAXAR in clinical trials and post marketing surveillance. Monitor patients receiving BALFAXAR for signs and symptoms of thromboembolic events. *[see Warnings and Precautions (5.2)]*.**
- **BALFAXAR may not be suitable in patients with thromboembolic events in the prior 3 months. *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

BALFAXAR (prothrombin complex concentrate, human-lans) 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.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dosage

- Measurement of INR prior to treatment and close to the time of dosing is important because coagulation factors may be unstable in patients with need for an urgent surgery and other invasive procedures.
- Individualize BALFAXAR dosing based on the patient's current pre-dose International Normalized Ratio (INR) value, and body weight (see Table 1).
- The actual potency per vial of Factor IX is stated on the carton. The potencies of Factors II, VII, IX and X, Proteins C and S are indicated as ranges.
- Administer Vitamin K concurrently to patients receiving BALFAXAR. Vitamin K is administered to maintain Vitamin K-dependent clotting factor levels once the effects of BALFAXAR have diminished.
- The safety and effectiveness of repeat dosing have not been established and it is not recommended.
- Dose ranging within pre-treatment INR groups has not been studied in randomized clinical trials of BALFAXAR.

Table 1 Dosage Required for Reversal of VKA Anticoagulation in Patients with Need for an Urgent Surgery/Invasive Procedure

Pre-treatment INR	2-< 4	4-6	> 6
Dose* of BALFAXAR (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

*Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-32 Factor IX units/mL after reconstitution. The actual potency for a 500 unit vial ranges from 400-640 units/vial. The actual potency for a 1000 unit vial ranges from 800-1280 units/vial.

† Units refer to International Units.

‡ Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

Example dosing calculation for 80 kg patient:

For example, an 80 kg patient with a baseline of INR of 5.0, the dose would be 2,800 Factor IX units of BALFAXAR, calculated as follows based on INR range of 4-6, see Table 1:

35 units of Factor IX/kg x 80 kg = 2,800 units of Factor IX required*

* For a vial with an actual potency of 30 units/mL Factor IX, 93 mL would be given (2,800 U/30 U per mL = 93 mL).

Monitor INR and clinical response during and after treatment. In clinical trials, BALFAXAR decreased the INR to ≤1.5 within 30 minutes in most subjects. The relationship between this or other INR values and clinical hemostasis in patients has not been established *[see Clinical Studies (14)]*.

2.2 Preparation and Reconstitution

BALFAXAR is provided with a transfer device (Nextaro®) for reconstitution of the lyophilized powder in diluent (sterile Water for Injection (sWFI)).

BALFAXAR is for single dose only. Do not re-use any of the components.

Inspect all components for physical integrity prior to use. Do not use products or components that appear damaged or broken.

Reconstitute BALFAXAR using aseptic technique for the procedure described below.

The product reconstitutes quickly (1 to 5 minutes) at room temperature (20°C to 25°C; 68°F to 77°F). As BALFAXAR contains no preservatives, the solution should be administered immediately after reconstitution, or within 8 hours, provided sterility is maintained. The reconstituted solution can be stored for up to 8 hours at room temperature (20°C to 25°C; 68°F to 77°F).

Instructions for Reconstitution:

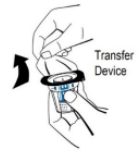


Figure 1

Figure 2

1. Ensure that the lyophilized powder and diluent vials are at room temperature (20°C to 25°C, 68°F to 77°F). This temperature should be maintained during reconstitution.
2. Remove the flip caps from the lyophilized powder and diluent vials and disinfect the rubber stoppers with an alcohol swab and allow to dry.
3. Open the transfer device package by peeling off the lid (*Figure 1*). To maintain sterility, do not remove the transfer device from the blister package and do not touch the spike.
4. Place the diluent vial on an even, clean surface and hold it firmly. Without removing the blister package, place the blue part of the transfer device on top of the diluent vial and press straight and firmly down until it snaps into place (*Figure 2*). Do not twist while attaching.

© 2023 Octapharma USA Inc. All rights reserved.

Figure 3

5. While holding onto the diluent vial, carefully remove the blister package from the transfer device by pulling vertically upwards. Make sure to leave the transfer device attached firmly to the diluent vial (*Figure 3*).

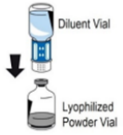


Figure 4

6. Place the lyophilized powder vial on an even, clean surface and hold it firmly. Take the diluent vial with the attached transfer device and turn it upside down. Place the white part of the transfer device connector on top of the powder vial and press firmly down until it snaps into place (*Figure 4*). Do not twist while attaching. The diluent will flow automatically into the powder vial.

Note:
The transfer device must be attached to the diluent vial first and then to the lyophilized powder vial. Otherwise, loss of vacuum occurs, and transfer of the diluent does not take place. If diluent is not completely transferred to the lyophilized powder vial during this process, contact your Octapharma representative.

Figure 5

7. With both vials still attached, gently swirl the product vial until the product is fully dissolved. To avoid foam formation, do not shake the vial. BALFAXAR dissolves quickly at room temperature (20°C to 25°C; 68°F to 77°F) and is a clear solution that may be colorless to slightly blue. Unscrew the transfer device counterclockwise into two parts (*Figure 5*). Do not touch the luer lock connector.
8. Dispose of the empty diluent vial together with the blue part of the transfer device.

Reconstituted products should be inspected visually for particulate matter. Do not use solutions that are cloudy or have deposits.

If the lyophilized powder fails to dissolve completely or an aggregate is formed, do not use the preparation.
After reconstitution, administration should begin promptly or within 8 hours, provided sterility is maintained.
If the same patient is to receive more than one vial, you may pool the contents of multiple vials, provided sterility is maintained. Use a separate unused transfer device for the reconstitution of each product vial.

2.3 Administration

BALFAXAR is for intravenous use after reconstitution only.

Do not mix with other medicinal products; administer through a separate infusion line. The infusion line may be flushed with normal saline before and after administration of BALFAXAR.

Instructions for Infusion:

Figure 6

1. Attach a syringe to the luer lock outlet on the white part of the transfer device (Figure 6).

Figure 7

2. Turn the vial upside down and draw the solution into the syringe (*Figure 7*).

Figure 8

3. Once the solution has been transferred, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and remove the syringe from the transfer device (*Figure 8*).
4. Dispose of the white part of the transfer device together with the empty vial.
5. Attach a suitable administration set to the luer adapter of the syringe.
6. Disinfect the intended injection site appropriately.
7. Administer by intravenous 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). No blood should enter the syringe due to the risk of fibrin clot formation.

Any unused product or waste material should be disposed of immediately in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

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.

4 CONTRAINDICATIONS

- Known anaphylactic or severe systemic reactions to BALFAXAR or any of the components of the product. For a complete listing of ingredients, [*see Description (11)*].
- Known allergy to heparin or history of heparin-induced thrombocytopenia (HIT).
- IgA deficient patients with known antibodies against IgA.

© 2023 Octapharma USA Inc. All rights reserved.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

If severe allergic or anaphylactic-type reactions occur, immediately discontinue administration of BALFAXAR and initiate appropriate treatment. Therapeutic measures depend on the type and severity of the undesirable effect.

5.2 Thromboembolic Risk/Complications

There is a risk of thrombosis or disseminated intravascular coagulation when patients with acquired deficiency are treated with human prothrombin complex. [1] Patients given human prothrombin complex should be observed closely for signs or symptoms of disseminated intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, monitoring of signs and symptoms should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, patients with liver disease, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. The potential benefit of treatment should be weighed against the risk of complications. BALFAXAR may not be suitable in patients with thrombotic or thromboembolic events in the prior 3 months, as it has not been studied in these patients. Resumption of anticoagulation should be carefully considered following administration of BALFAXAR and vitamin K once the risk of thromboembolic events outweighs the risk of bleeding.

5.3 Transmissible Infectious Agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents e.g., viruses, the vCJD agent, and theoretically, CJD agent, cannot be completely eliminated. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus (HAV) and human parvovirus B19 (B19V).

B19V infections may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis, e.g., hemolytic anemia.

All suspected infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to Octapharma USA Inc. at 1-866-766-4860.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a prospective, randomized, controlled, double-blind, multicenter non-inferiority trial, 208 subjects who required reversal of vitamin K antagonist induced anticoagulation due to the need for urgent surgery were enrolled; 105 received BALFAXAR and 103 Kcentra. Subjects ranged in age from 31 years to 92 years. Adverse reactions for BALFAXAR and the comparator are described below.

Adverse Reactions

The most common adverse reactions observed in ≥ 3% subjects receiving BALFAXAR were procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting and catheter site related reaction.

In the post-surgical setting, serious adverse reactions in BALFAXAR treatment arm included cerebral infarction, and pulmonary embolism as well as hemorrhage, acute respiratory failure, shock, subdural hemorrhage. One subject experienced one serious adverse reaction, unstable angina assessed as related to BALFAXAR.

Adverse reactions are summarized for BALFAXAR and Kcentra in the following table:

Table 2 Adverse Reactions Reported in More Than 3% Subjects Following BALFAXAR or Kcentra Administration

System Organ Class Preferred Term	BALFAXAR Subjects (N=105) n (%)	Kcentra Subjects (N=103) n (%)
Blood and lymphatic system disorders		
Anemia	6 (5.7%)	6 (5.8%)
Gastrointestinal disorders		
Abdominal pain	3 (2.9%)	5 (4.9%)
General disorders and administration site conditions		
Asthenia	13 (12.4%)	18 (17.5%)
Catheter site related reaction	4 (3.8%)	2 (1.9%)
Injury, poisoning and procedural complications		
Postoperative wound complication	15 (14.3%)	15 (14.6%)
Procedural pain	50 (47.6%)	50 (48.5%)
Procedural vomiting	4 (3.8%)	0
Suture related complication	2 (1.9%)	4 (3.9%)
Investigations		
Blood pressure increased	0	5 (4.9%)
Body temperature increased	0	4 (3.9%)
Renal and urinary disorders		
Dysuria	5 (4.8%)	2 (1.9%)

Deaths

There were a total of four deaths (3.8%) in the BALFAXAR group between 22 and 45 days post surgery, with one (1%) additional death occurring on day 47 just after completion of the study reporting period and one (1%) death in the Kcentra group 10 days after treatment. No deaths were considered to be related to study treatment.

Thromboembolic Events

There were three subjects (2.9%) with BALFAXAR who experienced four thromboembolic events in the randomized controlled trial in urgent surgery; cerebral infarction, pulmonary embolism, unstable angina and myocardial ischemia. The number of thromboembolic adverse reactions assessed as at least possibly related to study treatment was one (1%) with BALFAXAR (unstable angina). There were no thromboembolic events observed in the Kcentra treatment arm.

The following serious adverse reactions are described below and/or elsewhere in the labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions (5.1)*]
- Arterial and venous thromboembolic complications [*see Boxed Warning and Warnings and Precautions (5.2)*]
- Possible Transmission of Infectious Agents [*see Warnings and Precautions (5.3)*]

6.2 Postmarketing Experience

Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been reported during postmarketing use of BALFAXAR outside the US since 2003:

Table 3 Adverse Reactions Reported During Post-Marketing Use of BALFAXAR

Immune system disorders Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity reaction
Nervous system disorders Cerebrovascular accident, headache, paresthesia, tremor
Cardiac disorders Bradycardia, tachycardia, cardiac arrest
Vascular disorders Thromboembolic events, circulatory collapse, hypotension, hypertension

© 2023 Octapharma USA Inc. All rights reserved.

Respiratory, thoracic and mediastinal disorders Dyspnea, respiratory failure
Gastrointestinal disorders Nausea
Skin and subcutaneous tissue disorders Urticaria, rash, pruritus
General disorders and administration site conditions Fever, chills

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at 1-866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with BALFAXAR use in pregnancy to inform on drug-associated risk. Animal reproduction studies have not been conducted with BALFAXAR. It is not known whether BALFAXAR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the excretion of BALFAXAR in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BALFAXAR and any potential adverse effects on the breastfed child from BALFAXAR or from the underlying maternal condition.

8.4 Pediatric Use

The efficacy and safety of BALFAXAR have not been evaluated in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects (105) with need for an urgent surgery/invasive procedure treated with BALFAXAR to reverse VKA anticoagulation, 59% were 65 years old or greater and 20% were 75 years old or greater. There is no evidence to suggest that BALFAXAR use in the geriatric population is associated with differences in safety or effectiveness.

11 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. The actual potency printed on the vial label represents the potency of Factor IX. BALFAXAR is sterile, endotoxin-free, and does not contain preservatives. No albumin is added as a stabilizer, and the excipients are heparin and sodium citrate. The diluent for reconstitution of the lyophilized powder is sterile Water for Injection.

The composition of BALFAXAR is as follows:

Component	Potency Range for 500 IU vial	Potency Range for 1000 IU vial
Human Coagulation Factor II	340-500 IU	680-1000 IU
Human Coagulation Factor VII	240-400 IU	480-800 IU
Human Coagulation Factor IX	400-640 IU	800-1280 IU
Human Coagulation Factor X	300-540 IU	600-1080 IU
Protein C	320-560 IU	640-1120 IU
Protein S	240-600 IU	480-1200 IU
Heparin	80-384 IU	160-768 IU
Sodium Citrate	16.8-23.4 mmol/L	16.8-23.4 mmol/L

All human plasma used in the manufacture of BALFAXAR is obtained from U.S. 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 B19V to exclude donations with high titers. The limit for the titer of B19V DNA in the manufacturing pool is set not to exceed 10^4 IU/mL. Only plasma that passed virus screening is used for production.

The BALFAXAR manufacturing process has the capability to clear viruses by a solvent/detergent (S/D) virus inactivation step and a virus removal nanofiltration step. The mean cumulative virus reduction factors of these steps are summarized in Table 4.

Table 4 Virus Reduction During BALFAXAR Manufacturing

Production Step	Virus Reduction Factor [$\log_{10}$]				
	Enveloped Viruses			Non-Enveloped Viruses	
	HIV-1	BVDV	PRV	HAV	PPV
S/D treatment	≥ 4.35	≥ 5.96	≥ 5.77	n.a.	n.a.
Nanofiltration (Planova 20N or Pegasus SV4)	≥ 4.58	≥ 5.01	≥ 6.01	≥ 5.24	3.98
Global Reduction Factor	**≥ 8.93**	**≥ 10.97**	**≥ 11.78**	**≥ 5.24**	**3.98**

n.a.: not applicable
BVDV: Bovine Viral Diarrhea Virus, model for HCV
PRV: Pseudorabies Virus, model for large enveloped DNA viruses, e.g., HBV
PPV: Porcine Parvovirus, model for B19V

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The administration of BALFAXAR provides a rapid increase in plasma levels of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX) and antithrombotic proteins C and S. Together they are referred to/known as the prothrombin complex. [2; 3] BALFAXAR can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

12.2 Pharmacodynamics

In the randomized controlled trial in urgent surgery, the INR was determined at varying time points after the end of infusion. The median INR was 3.0 prior to the infusion and dropped to a median value of 1.30 by the 30-minute time point after the end of infusion. After 24 hours it was 1.25 in the BALFAXAR group (see Table 5).

The relationship between these or other INR values and clinical hemostasis in patients has not been established *[see Clinical Studies (14)]*.

Table 5 Median INR (Min-Max) After End of Infusion in Urgent Surgery RCT

Treatment	Baseline	30 min	2 hr	4 hr	12 hr	24 hr
BALFAXAR (N=105)	3.05 (2.0 - 21.1)	1.30 (1.0 – 3.1)	1.28 (1.0 - 2.5)	1.30 (1.0 - 2.0)	1.30 (0.9 - 2.7)	1.25 (0.8 - 3.4)

© 2023 Octapharma USA Inc. All rights reserved.

12.3 Pharmacokinetics

Since BALFAXAR is given intravenously, bioavailability is proportional to the dose administered. BALFAXAR is distributed, metabolized, and excreted in the same manner as the endogenous proteins (see Table 6).

Table 6 Pharmacokinetic Parameters and Recovery of Coagulation Factors, Protein C and Protein S

Parameter	FII	FVII	FIX	FX	Protein C	Protein S
C_{max} (%)	62.42/1.33 (37.00-118.00)	30.58/1.55 (13.00-81.00)	57.57/1.55 (27.00-130.00)	51.03/1.41 (30.00-120.00)	59.95/1.35 (38.00-109.00)	63.20/1.39 (30.00-115.00)
$C_{max,norm}$ (%/IU/kg)	2.38/1.23 (1.38-2.96)	1.16/1.51 (0.48-2.11)	2.19/1.65 (0.84-4.71)	1.94/1.26 (1.08-2.74)	2.28/1.31 (1.17-3.45)	2.41/1.41 (0.90-3.95)
Incremental Recovery** (%/IU/kg)	1.73/1.33 (0.81-2.42)	0.68/1.88 (0.11-1.62)	1.17/1.83 (0.26-2.52)	1.47/1.34 (0.73-2.38)	1.25/0.54* (0.00-2.22)	1.47/1.52 (0.59-2.35)
Absolute Recovery*** (%)	75.70/1.34 (32.65-116.98)	29.64/1.90 (4.45-78.35)	51.36/1.82 (13.54-115.58)	64.39/1.37 (29.68-114.8)	54.95/24.60* (0.00-107.04)	64.26/1.55 (23.74-113.66)
t_{max}	0.17 (0.17-3.00)	0.17 (0.17-1.00)	0.50 (0.17-3.00)	0.17 (0.17-3.00)	0.17 (0.00-3.00)	0.17 (0.17-3.00)

Note: Values reported as geometric mean/geometric SDs (range), except for t_{max} which is reported as median (min-max)
*Mean values SD (due to zero values, the geometric mean could not be calculated)
**The incremental recovery is defined as the rise in the plasma concentrations (%) achieved with 1 IU BALFAXAR/kg BW.
***The absolute recovery is defined as the rise in the plasma concentrations (%) achieved by the dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of BALFAXAR or studies to determine the effects of BALFAXAR on genotoxicity or fertility have not been performed.

14 CLINICAL STUDIES

The efficacy of BALFAXAR was assessed in a randomized, double-blind, multicenter study in comparison to Kcentra, for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery. A total of 208 subjects with acquired coagulation factor deficiency due to oral Vitamin K antagonist therapy were randomized to a single dose of BALFAXAR (n=105) or Kcentra (n=103). The doses of BALFAXAR and Kcentra based on the nominal Factor IX content (25 units/kg, 35 units/kg, or 50 units/kg) were calculated according to the patient's baseline INR (2-< 4, 4-6, >6, respectively). The observation period lasted for 45 days post-surgery. The primary endpoint was hemostatic efficacy rating at the end of the surgery assessed by the Independent Endpoint Adjudication Board (IEAB). The study was stopped early due to statistically significant efficacy results at the pre-specified interim analysis, where 94.6% (88/93) of the subjects in the BALFAXAR group and 93.5% (86/92) of the subjects in the Kcentra group achieved effective hemostasis (Table 7). The non-inferiority analysis for the proportion difference (98% CI) of 1.1% (-9.2%, 11.5%) was statistically significant (p<0.001) indicating that BALFAXAR was non-inferior to Kcentra. The lower bound of the CI was above the pre-specified noninferiority margin of -15%, indicating that BALFAXAR was non-inferior to Kcentra. At the conclusion of the study, the updated proportions of subjects with effective hemostasis were 94.3 % (99/105) in the BALFAXAR group and 94.2 % (97/103) in the Kcentra group (Table 7), resulting in a difference (95% CI) of 0.1% (-8.0%, 8.2%).

Table 7 Rating of Hemostatic Efficacy in Urgent Surgery RCT

Effective hemostasis	No. (%) of subjects		Proportion difference
	BALFAXAR	Kcentra	BALFAXAR vs. Kcentra
Interim analysis	88/93 (94.6%)	86/92 (93.5%)	1.1%, 98% CI: (-9.2%, 11.5%)*
Final analysis**	99/105 (94.3%)	97/103 (94.2%)	0.1%, 95% CI: (-8.0%, 8.2%)

CI = confidence interval N = number of subjects

* Met pre-specified non-inferiority criterion (Margin used -15% and p<0.001, statistically significant at pre-specified alpha level of 0.01)
** Descriptive analysis of all subjects in the study including an overrun of subjects during the decision making at the interim analysis.

Mean (SD) baseline (i.e., within 3 hours prior to BALFAXAR or Kcentra infusion) INR was 3.96 (2.77) in the BALFAXAR group and 3.56 (1.82) in the Kcentra group. The proportion of patients achieving an INR ≤1.5 as measured 30 minutes after the end of the infusion was 78.1% in the BALFAXAR group versus 71.8% in the Kcentra group (proportion difference of 6.3%; 95% CI: -5.5%, 18.0%). Overall, 72.1% of patients had vitamin K administered, with a median dose of 10 mg in both groups (Table 8).

Table 8 Decrease of INR (to 1.5 or Less at 30 Minutes after End of Infusion) in Urgent Surgery RCT

Rating	No. (%) of subjects		Proportion difference BALFAXAR vs Kcentra (95% CI for difference)
	BALFAXAR (N=105)	Kcentra (N=103)	
Decrease of INR to ≤ 1.5 at 30 min	82 (78.1)	74 (71.8)	6.3% (-5.5%, 18.0%)

The median dose of BALFAXAR/ Kcentra was 25 IU of Factor IX/kg body weight in both treatment groups, ranging from 16 IU/kg to 50 IU/kg in the BALFAXAR group and 15 IU/kg to 50 IU/kg in the Kcentra group. The median duration of the infusion was 12 minutes in the BALFAXAR group (ranging from 8 to 50 minutes) and 13 minutes (ranging from 7 to 30 minutes) in the Kcentra group.

15 REFERENCES

1. Koehler M: Thrombogenicity of prothrombin complex concentrates. Thrombosis Research 1999;95:S13-S17.
2. Warkentin TE, Crowther MA: Reversing anticoagulants both old and new. Can.J. Anaesth. 2002;49:S11-S25.
3. Ansell J, Hirsh J, Poller L, et al: The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:204S-233S.

16 HOW SUPPLIED/STORAGE AND HANDLING

BALFAXAR is supplied in single-dose vials.

Carton NDC Number	Container (Vial) NDC Number	Size	Color coding
68982-261-01	68982-261-81	500 IU Range FIX in 20 mL	purple
68982-261-02	68982-261-82	1000 IU Range FIX in 40 mL	green

- BALFAXAR is supplied in a package with a single-dose vial of lyophilized powder and a vial of diluent (sterile Water for Injection), together with a transfer device.
- Components used in the packaging of BALFAXAR are not made with natural rubber latex.
- Store BALFAXAR for up to 36 months at 2°C to 25°C (36°F to 77°F) from the date of manufacture. Do not freeze.
- Do not use beyond the expiration date on the vial label and carton.
- Store the vial in the original package to protect it from light.
- Reconstitute the BALFAXAR powder only directly before use. Use the solution immediately after reconstitution. However, if it is not administered immediately, the reconstituted solution can be stored for up to 8 hours at room temperature (20°C to 25°C; 68°F to 77°F), provided sterility of the stored product is maintained. Discard partially used vials.

© 2023 Octapharma USA Inc. All rights reserved.

Appendix A | Prescribing Information (continued)

17 PATIENT COUNSELING INFORMATION

- Inform patients of the signs and symptoms of allergic hypersensitivity reactions, such as urticaria, rash, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of BALFAXAR. [*see Warnings and Precautions (5.1)*].
- Inform patients of signs and symptoms of thrombosis, such as limb or abdomen swelling and/or pain, chest pain or pressure, shortness of breath, loss of sensation or motor power, altered consciousness, vision, or speech. [*see Warnings and Precautions (5.2)*].
- Inform patients that, because BALFAXAR is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. [*see Warnings and Precautions (5.3), Description (11)*].

Manufactured by:
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
1100 Vienna, Austria
U.S. License No. 1646

Distributed by:
Octapharma USA Inc.
117 W Century Road
Paramus, NJ 07652

Appendix B | References

1. Balfaxar [prescribing information]. Paramus, NJ: Octapharma USA; 2023.
2. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation. 2003;107(12):1692-1711.
3. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. Arch Intern Med. 2007;167(13):1414-1419.
4. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. CMAJ. 2013;185(2):E121-E127.
5. ASGE Standards of Practice Committee, Acosta RD, Abraham NS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy [published correction appears in Gastrointest Endosc. 2016 Mar;83(3):678]. Gastrointest Endosc. 2016;83(1):3-16. doi:10.1016/j.gie.2015.09.035
6. Baugh CW, Levine M, Cornutt D, et al. Anticoagulant reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel. Ann Emerg Med. 2020;76(4):470-485. https://doi.org/10.1016/j.annemergmed.2019.09.00
7. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding. Eur J Anaesthesiol. 2017;34(6):332-395. https://doi.org/10.1097/eja.0000000000000630
8. Octapharma Data on File 2023.
9. Becattini C, Vedovati MC, Agnelli G. Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: a review of the literature. Thromb Res. 2012;129(3):392-400.
10. DeWald TA, Washam JB, Becker RC. Anticoagulants: pharmacokinetics, mechanisms of action, and indications. Neurosurg Clin N Am. 2018;29(4):503-515.
11. Green B, Mendes RA, Van der Valk R, et al. Novel anticoagulants - an update on the latest developments and management for clinicians treating patients on these drugs. J Oral Pathol Med. 2016;45(8):551-556.

© 2023 Octapharma USA Inc. All rights reserved.

12. Harbrecht U. Old and new anticoagulants. Hamostaseologie. 2011;31(1):21-27.
13. Levi M. Emergency reversal of antithrombotic treatment. Intern Emerg Med. 2009;4(2):137-145.
14. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy. Chest. 2012;141(2). https://doi.org/10.1378/chest.11-2295
15. Sikorska J, Uprichard J. Direct oral anticoagulants: a quick guide. Euro Cardiol. 2017;12(1):40-45.
16. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol. 2013;112(8):1142-1147.
17. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-220.
18. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. J Intern Med. 2013;274(5):461-468.
19. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. Circ Cardiovasc Qual Outcomes. 2012;5(5):615-621. doi:10.1161/CIRCOUTCOMES.112.967299
20. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808. doi:10.1056/NEJMoa1302507
21. Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol. 2023;20(4):248-262. doi:10.1038/s41569-022-00787-6
22. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association [published correction appears in Circulation. 2022 Sep 6;146(10):e141]. Circulation. 2022;145(8):e153-e639. doi:10.1161/CIR.0000000000001052
23. Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: the ISAM study. J Thromb Thrombolysis. 2006;21(1):73-77. doi:10.1007/s11239-006-5580-y
24. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee [published correction appears in J Am Coll Cardiol. 2021 Jun 1;77(21):2760]. J Am Coll Cardiol. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053
25. Geller AI, Shehab N, Lovegrove MC, et al. Bleeding related to oral anticoagulants: Trends in US emergency department visits, 2016-2020. Thromb Res. 2023;225:110-115.
26. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e44S-e88S. doi:10.1378/chest.11-2292
27. Green D. Coagulation cascade. Hemodial Int. 2006;10 Suppl 2:S2-S4. doi:10.1111/j.1542-4758.2006.00119.x
28. Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. Crit Rev Biochem Mol Biol. 2015;50(4):326-336. doi:10.3109/10409238.2015.1050550
29. Trujillo TC. Emerging anticoagulants for venous thromboembolism prevention. Am J Health Syst Pharm. 2010;67(10 Suppl 6):S17-S25.
30. Coumadin [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Co; 2017.
31. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchel H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M; RE-LY Investigators. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation. 2012 Jul 17;126(3):343-8
32. Hunt BJ, Levi M. Urgent reversal of vitamin K antagonists. BMJ. 2018;360:j5424.
33. Milling TJ, Jr., Refaai MA, Sarode R, et al. Safety of a four factor prothrombin complex concentrate versus plasma for vitamin K antagonist reversal: An integrated analysis of two phase IIIb clinical trials. Acad Emerg Med. 2016;23(4):466-475.
34. Marshall AL, Levine M, Howell ML, et al. Dose-associated pulmonary complication rates after fresh frozen plasma administration for warfarin reversal. J Thromb Haemost. 2016;14(2):324-330.
35. Christensen H, Cordonnier C, Korv J, et al. European Stroke Organisation Guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. Eur Stroke J. 2019;4(4):294-306.
36. Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. Mayo Clin Proc. 2007;82(1):82-92.
37. Milling TJ, Refaai MA, Sarode R, et al. Safety of a four-factor prothrombin complex concentrate versus plasma for vitamin K antagonist reversal: an integrated analysis of two phase IIIb clinical trials. Acad Emerg Med. 2016;23(4):466-475. https://doi.org/10.1111/acem.12911
38. Octapharma Data on File 2023

Kcentra is a registered trademark of CSL Behring GmbH
nextaro is a registered trademark of sfm medical devices
Mix2Vial is a registered trademark of West Pharmaceutical Services

© 2023 Octapharma USA Inc. All rights reserved.

39. Lubetsky A, Hoffman R, Zimlichman R, et al. Efficacy and safety of a prothrombin complex concentrate (Octaplex) for rapid reversal of oral anticoagulation. Thromb Res. 2004;113(6):371-378.

40. Riess H, Meier-Hellmann A, Motsch J, et al. Prothrombin complex concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation. Thromb Res. 2007;121(1):9-16.

41. Franken T, Rees W, Hübner N, et al. Octaplex in routine clinical use for prophylaxis and therapy of bleeding in patients with prothrombin complex factor deficiency. Crit Care. 2007;11(Suppl 2):P376.

42. Sarode R, Goldstein J, Simonian G, et al. *JAMA Network Open*. 2024;7(8):e2424758. doi:10.1001/jamanetworkopen.2024.24758

Kcentra is a registered trademark of CSL Behring GmbH
nextaro is a registered trademark of sfm medical devices
Mix2Vial is a registered trademark of West Pharmaceutical Services

© 2023 Octapharma USA Inc. All rights reserved.

©2026. Octapharma USA, Inc. All rights reserved.
Date of preparation: 01/2026. BALF-0267