# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

**Beriplex® P/N 250,** powder and solvent for solution for injection.
**Beriplex® P/N 500,** powder and solvent for solution for injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Beriplex is presented as powder and solvent for solution for injection containing human prothrombin complex. The product nominally contains the following IU of the human coagulation factors tabled below:

| **Name of the ingredients** | **Content after reconstitution (IU/ml)** | **Beriplex P/N 250 content per vial (IU)** | **Beriplex P/N 500 content per vial (IU)** |
|---|---|---|---|
| **Active Ingredients** | | | |
| Human coagulation factor II | 20 – 48 | 200 – 480 | 400 – 960 |
| Human coagulation factor VII | 10 – 25 | 100 – 250 | 200 – 500 |
| Human coagulation factor IX | 20 – 31 | 200 – 310 | 400 – 620 |
| Human coagulation factor X | 22 – 60 | 220 – 600 | 440 – 1200 |
| **Further active ingredients** | | | |
| Protein C | 15 – 45 | 150 – 450 | 300 – 900 |
| Protein S Antigen | 12 – 38 | 120 – 380 | 240 – 760 |

The total protein content is 6 – 14 mg/ml of reconstituted solution.

The specific activity of factor IX is 2.5 IU per mg total protein.

The activities of all coagulation factors as well as Protein C and S (antigen) have been tested according to the current valid international WHO-Standards.

Excipients with known effect:
Sodium up to 343 mg (approximately 15 mmol) per 100 ml solution.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White or slightly coloured powder or friable solid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

### 4.2 Posology and method of administration

***Posology***

Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-lives of the respective coagulation factors in the prothrombin complex (see section 5.2). Individual dosage requirements can only be identified on the basis of regular determinations of the individual plasma levels of the coagulation factors of interest, or on global tests of the prothrombin complex levels (INR, Quick's test), and a continuous monitoring of the clinical condition of the patient.

In case of major surgical interventions, precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

- **Bleeding and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.**

  The dose will depend on the INR before treatment and the targeted INR. The pre-treatment INR should be measured as close as possible to the time of dosing in order to calculate the appropriate dose of Beriplex. In the following table approximate doses (ml/kg body weight of the reconstituted product and IU Factor IX/kg b.w.) required for normalisation of INR (e.g. ≤ 1.3) at different initial INR levels are given.

| Pre-treatment INR | 2.0 – 3.9 | 4.0 – 6.0 | > 6.0 |
|---|---|---|---|
| Approximate dose ml/kg body weight | 1 | 1.4 | 2 |
| Approximate dose IU (Factor IX)/kg body weight | 25 | 35 | 50 |

Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, the maximum single dose (IU of Factor IX) should therefore not exceed 2500 IU for an INR of 2.0 - 3.9, 3500 IU for an INR of 4.0 - 6.0 and 5000 IU for an INR of > 6.0.
The correction of the vitamin K antagonist-induced impairment of haemostasis is commonly reached approximately 30 minutes after the injection.
The simultaneous administration of vitamin K should be considered in patients receiving Beriplex for urgent reversal of vitamin K antagonists since vitamin K usually takes effect within 4 - 6 hours. Repeated dosing with Beriplex for patients requiring urgent reversal of vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.

These recommendations are based on data from clinical studies with a limited number of subjects. Recovery and the duration of effect may vary, therefore monitoring of INR during treatment is mandatory.

*Paediatric population*

The safety and efficacy of Beriplex in children and adolescents has not yet been established in controlled clinical studies (see section 4.4).

*Older population*

The posology and method of administration in older people (> 65 years) is equivalent to the general recommendations.

***Method of administration***

For instructions on reconstitution of the medicinal product before administration, see section 6.6. The reconstituted solution should be administered intravenously (not more than 3 IU/kg/minute, max. 210 IU/minute, approximately 8 ml/minute).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In the case of disseminated intravascular coagulation, prothrombin complex-preparations may only be applied after termination of the consumptive state.

Known history of heparin-induced thrombocytopenia.

## 4.4 Special warnings and precautions for use

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K-dependent coagulation factors (e.g. as induced by treatment of vitamin K antagonists), Beriplex should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleedings or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient.

Patients receiving a vitamin K antagonist may have an underlying hypercoaguable state and infusion of human prothrombin complex may exacerbate this.

If allergic or anaphylactic-type reactions occur, the administration of Beriplex has to be stopped immediately (e.g. discontinue injection) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed.

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency, are treated with human prothrombin complex particularly with repeated dosing. The risk may be higher in treatment of isolated factor VII deficiency, since the other vitamin K-dependent coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal. 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, close monitoring should be exercised when administering Beriplex to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients per- or postoperatively, to neonates or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency. In each of these situations, the potential benefit of treatment with Beriplex should be weighed against the potential risk of such complications.

In patients with disseminated intravascular coagulation, it may, under certain circumstances, be necessary to substitute the coagulation factors of the prothrombin complex. This substitution may, however, only be carried out after termination of the consumptive state (e.g. by treatment of the underlying cause, persistent normalization of the antithrombin III level).

Reversing vitamin K antagonists exposes patients to the thromboembolic risk of the underlying disease. Resumption of anticoagulation should be carefully considered as soon as possible.

Undesirable reactions may include the development of heparin-induced thrombocytopenia, type II (HIT, type II). Characteristic signs of HIT are a platelet count drop > 50 per cent and/or the occurrence of new or unexplained thromboembolic complications during heparin therapy. Onset is typically from 4 to 14 days after initiation of heparin therapy but may occur within 10 hours in patients recently exposed to heparin (within the previous 100 days).

No data are available regarding the use of Beriplex in case of perinatal bleeding due to vitamin K deficiency in neonates.

Beriplex contains up to 343 mg sodium (approximately 15 mmol) per 100 ml. To be taken into consideration by patients on a controlled sodium diet.

***Virus safety***
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 infective agents cannot be totally excluded. 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) and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

It is strongly recommended that every time that Beriplex is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

## 4.5 Interaction with other medicinal products and other forms of interaction

Human prothrombin complex products neutralise the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known.

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken into account.

## 4.6 Fertility, pregnancy and lactation

***Pregnancy and Breastfeeding***

The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established. Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

***Fertility***
No fertility data are available.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

Summary of the Safety Profile
Allergic or anaphylactic-type reactions have been uncommonly observed, including severe anaphylactic reactions (see section 4.4).
Replacement therapy may lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. In such cases, it is recommended to contact a specialised haemophilia center for guidance. Anaphylactic reactions have been observed in patients with antibodies to factors contained in Beriplex.

Increase in body temperature has been commonly observed.

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section 4.4).

Tabulated list of adverse drug reactions of Beriplex
The following adverse reactions are based on clinical trial data, post marketing experience as well as scientific literature.

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been based on clinical trial data, according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) or not known (cannot be estimated from the available data).

| **MedDRA Standard System Organ Class** | **Adverse Drug Reaction by PT** | **Frequency** |
|---|---|---|
| Vascular disorders and other SOCs | Thromboembolic events* | common |

| MedDRA Standard System Organ Class | Adverse Drug Reaction by PT | Frequency |
|---|---|---|
| Blood and lymphatic system disorders | Disseminated intravascular coagulation | not known |
| Immune system disorders | Hypersensitivity or allergic reactions | uncommon |
| | Anaphylactic reactions including anaphylactic shock | not known |
| | Development of antibodies | not known |
| Nervous system disorders | Headache | common |
| General disorders and administration site conditions | Body temperature increased | common |

*including cases with fatal outcome

For safety with respect to transmissible agents, see section 4.4.

Paediatric population
No data are available regarding the use of Beriplex in paediatric population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at:
PV-IL@cslbehring.com

## 4.9 Overdose

To avoid overdosage, regular monitoring of the coagulation status is indicated during the treatment as the use of high doses of prothrombin complex concentrate (overdosage) has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. In case of overdosage the risk of thromboembolic complications or disseminated intravascular coagulation is enhanced in patients at risk of these complications.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors II, VII, IX and X in combination
ATC code: B02B D01

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly called the prothrombin complex. In addition to the coagulation factors Beriplex contains the vitamin K dependent coagulation inhibitors Protein C and Protein S.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue thromboplastin factor-factor VIIa complex activates coagulation factors IX and X, whereby factor IXa and Xa are formed. With further activation of the coagulation cascade, prothrombin (factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of the primary haemostasis.

Isolated severe deficiency of factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis. Isolated deficiency of factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia.

The further ingredients, the coagulation inhibitors Protein C and Protein S, are also synthesized in the liver. The biological activity of Protein C is enforced by the cofactor Protein S.

Activated Protein C inhibits the coagulation by inactivating the coagulation factors Va and VIIIa. Protein S as cofactor of Protein C supports the inactivation of the coagulation. Protein C deficiency is associated with an increased risk of thrombosis.

Acquired deficiency of the vitamin K-dependent coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K-dependent coagulation factors and a clinical relevant bleeding tendency. However this is often complex due to a simultaneously ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K-dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

## 5.2 Pharmacokinetic properties

Pharmacokinetic and *in-vivo* recovery data were generated in a healthy volunteer study (N = 15) and in two studies in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleedings (N = 98, N = 43).

Healthy Volunteer Study:
15 healthy volunteers were administered 50 IU/kg of Beriplex. The IVR is the increase in measurable factor levels in plasma (IU/ml) that may be expected following an infusion of factors (IU/kg) administered as a dose of Beriplex. Incremental IVRs for Factors II, VII, IX, X, and Proteins C and S were assessed. All maximum component levels occurred within the 3-hour time interval. Mean incremental IVRs ranged between 0.016 IU/ml for Factor IX and 0.028 for Protein C.
Median plasma half-lives and incremental IVR are indicated as follows:

| Parameter | Median plasma half-lives (range)/hours | Incremental IVR (IU/ml per IU/kg b.w.) | |
|---|---|---|---|
| | | Geometric Mean | 90 % CI† |
| Factor II | 60 (25 – 135) | 0.022 | (0.020 – 0.023) |
| Factor VII | 4 (2 – 9) | 0.024 | (0.023 – 0.026) |
| Factor IX | 17 (10 – 127) * | 0.016 | (0.014 – 0.018) |
| Factor X | 31 (17 – 44) | 0.021 | (0.020 – 0.023) |
| Protein C | 47 (9 – 122) * | 0.028 | (0.027 – 0.030) |
| Protein S | 49 (33 – 83) * | 0.020 | (0.018 – 0.021) |

† Confidence Interval
* terminal half-life; two-compartment-model

Beriplex is distributed and metabolized in the organism in the same way as the endogenous coagulation factors II, VII, IX and X.

Intravenous administration means that the preparation is available immediately; bioavailability is proportional to the dose administered.

Study in reversal of vitamin K antagonist treatment for acute major bleeding:
The mean *in-vivo* recovery (IVR) was calculated in 98 subjects who received Beriplex for treatment of bleeding during vitamin K antagonist treatment. The incremental IVR responses ranged between 0.016 IU/ml for Factor VII and 0.019 IU/ml for Protein C.

Study in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleeding:
The mean *in-vivo* recovery (IVR) was calculated in 43 subjects who received Beriplex for treatment of bleeding or perioperative prophylaxis of bleedings during vitamin K antagonist

treatment. The intravenous administration of 1 IU/kg Beriplex increased plasma levels of the vitamin K dependent coagulation factors ranging from 0.013 to 0.023 IU/ml.

### 5.3 Preclinical safety data

Beriplex contains as active ingredients the factors of the prothrombin complex (factors II, VII, IX and X). They are derived from human plasma and act like endogenous constituents of plasma.

Single dose toxicity studies with the predecessing pasteurized but not nanofiltrated product showed moderate toxicity in mice after the administration of 200 IU/kg, the highest dose tested. A single i.v. dose of the pasteurized and nanofiltrated product of up to 100 IU/kg was tolerated in rats. Preclinical studies with repeated dose applications (chronic toxicity, cancerogenicity and reproductive toxicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

The local tolerance after intravenous administration of Beriplex was shown in rabbits. A neoantigenicity study with rabbits has shown no indication of generation of a neoepitop due to the pasteurization process.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder:*
Sodium chloride
Human albumin
Sodium citrate
Heparin
Antithrombin III
HCl or NaOH (in small amounts for pH adjustment)

*Solvent:*
Water for injections

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (max. 25 °C). However, from a microbiological point of view, the product should be used immediately.

## 6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton, in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

*Beriplex P/N 250:*
Powder: Injection vial of colourless glass (Type II), sealed with latex-free infusion stopper (bromobutyl rubber), aluminium seal and plastic flip-off cap.
Solvent: 10 ml Water for injections in an injection vial of colourless glass (Type I), sealed with latex-free infusion stopper (chlorobutyl rubber), aluminium seal and plastic flip-off cap.
Injection device: 1 filter transfer device 20/20 (Mix2Vial)

*Beriplex P/N 500:*
Powder: Injection vial of colourless glass (Type II), sealed with latex-free infusion stopper (bromobutyl rubber), aluminium seal and plastic flip-off cap.
Solvent: 20 ml Water for injections in an injection vial of colourless glass (Type I), sealed with latex-free infusion stopper (chlorobutyl rubber), aluminium seal and plastic flip-off cap.
Injection device: 1 filter transfer device 20/20 (Mix2Vial)

Not all pack sizes may be marketed.

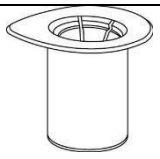
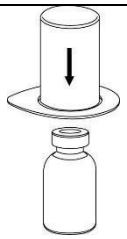
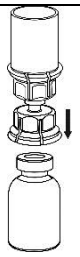
## 6.6 Special precautions for disposal and other handling

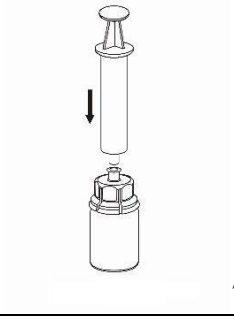
***Method of administration***

*General instructions*
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use solutions that are cloudy or have deposits.
- Reconstitution and withdrawal must be carried out under aseptic conditions.

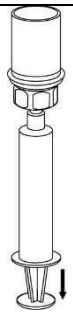
*Reconstitution*

Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

| | |
|---|---|
|  1 | 1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package! |
|  2 | 2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper. |
|  3 | 3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set. |
|  4 | 4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial. |
|  5 | 5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew counterclockwise the set carefully into two pieces.<br>Discard the solvent vial with the blue Mix2Vial adapter attached. |
|  6 | 6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. |

| | |
|---|---|
|  7 | 7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial. |

*Withdrawal and application*

| | |
|---|---|
|  8 | 8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly. |
|  9 | 9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise. |

Care should be taken that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots could therefore be administered to the patient.

In case more than one vial of Beriplex is required, it is possible to pool several vials of Beriplex for a single infusion via a commercially available infusion device.

The Beriplex solution must not be diluted.

The reconstituted solution should be administered by a separate injection / infusion line by slow intravenous injection, at a rate not exceeding 3 IU/kg/minute, max. 210 IU/minute, approximately 8 ml/minute.

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

## 7. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

## 8. REGISTRATION HOLDER

CSL BEHRING LTD.,
4 Dolev st., Ra'anana 4366204

## 9. REGISTRATION NUMBERS

BERIPLEX ® P/N 250 147 87 33308 00
BERIPLEX ® P/N 500 147 88 33309 00

Revised in September 2023 according to MoH guidelines.

CSL Behring