CSL Behring

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Beriplex® P/N 500

Powder and solvent for solution for injection.
Active ingredient: Human prothrombin complex (PCC)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Beriplex P/N 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 500 content per vial (IU)
Active Ingredients		
Human coagulation factor II	20 – 48	400 – 960
Human coagulation factor VII	10 – 25	200 – 500
Human coagulation factor IX	20 – 31	400 – 620
Human coagulation factor X	22 – 60	440 – 1200
Further active ingredients		
Protein C	15 – 45	300 – 900
Protein S	12 – 38	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.

Other ingredients
Powder:
Heparin
Human albumin
Human antithrombin III
Sodium chloride
Sodium citrate
HCl or NaOH (in small amounts for pH adjustment)
Solvent:
Water for injections

PHARMACEUTICAL FORM AND PRESENTATIONS

Pharmaceutical form
Powder and solvent for solution for injection.

Presentations
Beriplex P/N 500:
1 vacuum vial with dried substance
1 vial with 20 ml water for injections
1 filter transfer device 20/20
Beriplex P/N 250:
1 vacuum vial with dried substance
1 vial with 10 ml water for injections
1 filter transfer device 20/20

Not all pack sizes may be marketed.

PHARMACOTHERAPEUTIC GROUP

Antihaemorrhagics/Blood coagulation factors II, VII, IX and X in combination
ATC code: B02B D01

NAME AND ADDRESS OF THE MANUFACTURER AND MARKETING AUTHORISATION HOLDER

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

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.
– Treatment and perioperative prophylaxis of bleedings in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor products are not available.

CONTRAINDICATIONS

Known hypersensitivity to any of the components of the product.
Risk of thrombosis, angina pectoris, recent myocardial infarction (exception: life-threatening haemorrhages following overdosage of oral anticoagulants, and before induction of fibrinolytic therapy).
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.

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 P/N 500 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.
In congenital deficiency of any of the vitamin K-dependent factors, specific coagulation factor products should be used when available.
If allergic or anaphylactic-type reactions occur, the administration of Beriplex P/N 500 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 P/N 500 to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients 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 P/N 500 should be weighed against the potential risk of such complications. In patients with DIC and sepsis antithrombin III substitution should be considered prior to treatment with Beriplex P/N 500.
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).
When Beriplex P/N 500 is used to normalize impaired coagulation, prophylactic administration of heparin should be considered.
No data are available regarding the use of Beriplex P/N 500 in case of perinatal bleeding due to vitamin K deficiency in neonates.
Beriplex P/N 500 contains up to 343 mg sodium (approximately 15 mmol) per 100 ml. To be taken into consideration by patients on a controlled sodium diet.

Pregnancy and lactation
The safety of Beriplex P/N 500 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, Beriplex P/N 500 should be used during pregnancy and lactation only if clearly indicated.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and
- the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus, hepatitis C virus (inflammation of the liver), and for the non-enveloped virus hepatitis A (inflammation of the liver).
The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.
Parvovirus B19 infection may be serious
- for pregnant women (infection of the unborn child) and
- for individuals with a depressed immune system or with an increased production of red blood cells due to certain types of anaemia (e.g. sickle cell anaemia or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products.
It is strongly recommended that every time that Beriplex P/N 500 is given, your doctor should record the date of administration, the batch number and the injected volume.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

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.

Incompatibilities
Beriplex P/N 500 must not be mixed with other medicinal products, diluents or solvents.

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. 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).
The posology and method of administration in elderly people (> 65 years) is equivalent to the general recommendations.
There is no experience in children (see section "Special warnings and precautions for use").

– Treatment and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.
The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (ml/kg body weight of the reconstituted product and IU FIX/kg b.w.) required for normalisation of INR (e.g. ≤ 1.3) at different initial INR levels are given.

Initial 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

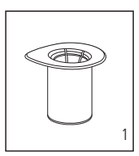
It is recommended that the maximum single dose should not exceed 5000 IU FIX.
The correction of the vitamin K antagonist-induced impairment of haemostasis is reached at the latest 30 minutes after the injection and will persist for approximately 6 – 8 hours. However, the effect of vitamin K, if administered simultaneously, is usually achieved within 4 – 6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.
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.
– Bleedings and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when specific coagulation factor products are not available.
The calculation of the required dosage of prothrombin complex concentrate is based on data from clinical studies:
- 1 IU of factor IX per kg body weight can be expected to raise the plasma factor IX activity by 1.3 % (0.013 IU/ml) of normal
- 1 IU of factor VII per kg body weight raises the plasma factor VII activity by 1.7 % (0.017 IU/ml) of normal
- 1 IU of factor II per kg body weight raises the plasma factor II activity by 1.9 % (0.019 IU/ml) of normal
- 1 IU of factor X per kg body weight raises the plasma factor X activity by 1.8 % (0.018 IU/ml) of normal.

The dose of a specific factor administered is expressed in International Units (IU), which are related to the current WHO standard for each factor. The activity in the plasma of a specific coagulation factor is expressed either as a percentage (relative to normal plasma) or in International Units (relative to the international standard for the specific coagulation factor).
One International Unit (IU) of a coagulation factor activity is equivalent to the quantity in one ml of the normal human plasma.
For example, the calculation of the required dosage of factor X is based on the finding that 1 International Unit (IU) of factor X per kg body weight raises the plasma factor X activity by 0.018 IU/ml.
The required dosage is determined using the following formula:
Required units = body weight [kg] x desired factor X rise [IU/ml] x 56 where 56 (ml/kg) is the reciprocal of the estimated recovery.
If the individual recovery is known, that value should be used for calculation.

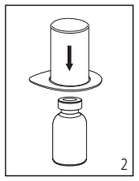
Overdose
To avoid overdosage, regular monitoring of the coagulation status is indicated during the treatment as the use of high doses of prothrombin complex concentrate (overdosage) has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis 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.

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.

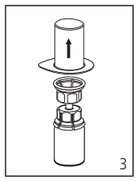
Reconstitution
Bring the solvent to room temperature. Ensure that product and solvent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.



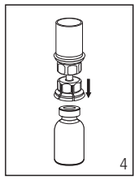
1. Open the Mix2Vial package by peeling away the lid.



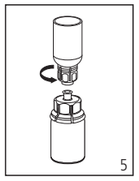
2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the package and push the blue end straight down through the solvent stopper.



3. Carefully remove the package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set.

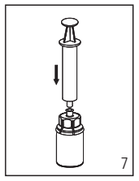


4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the transparent adapter straight down through the product vial stopper. The solvent will automatically flow into the product vial.



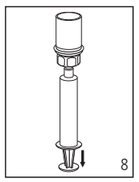
5. With one hand hold the product-side of the Mix2Vial set, hold the solvent-side with the other hand and unscrew the set into two pieces.
Discard the solvent vial with the blue part attached.

6. Gently swirl the product vial until the substance is fully dissolved. Do not shake.

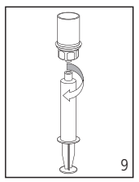


7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting. Inject air into the product vial.

Withdrawal and application



8. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.



9. Now that the concentrate has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the Mix2Vial set from the syringe.

The reconstituted solution should be administered intravenously (not more than 3 IU/kg/min, max. 210 IU/min, approximately 8 ml/min).
It has to be taken care 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 would therefore be administered to the patient.
The reconstituted solution should be administered by a separate infusion line.

UNDESIRABLE EFFECTS
If you experience reactions, especially those which are not mentioned in this package leaflet, please inform your doctor or pharmacist.
The following adverse reactions are based on post marketing experience as well as scientific literature. The following standard categories of frequency are used:
Very common: ≥ 1/10
Common: ≥ 1/100 and < 1/10
Uncommon: ≥ 1/1,000 and < 1/100
Rare: ≥ 1/10,000 and < 1/1,000
Very rare: < 1/10,000 (including reported single cases)
Renal and urinary disorders:
Nephrotic syndrome has been reported in single cases following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.
Vascular disorders:
There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section "Special warnings and precautions for use").
General disorders and administration site conditions:
Increase in body temperature is observed in very rare cases.
Immune system disorders:
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, angina pectoris, tingling, vomiting or wheezing) have been observed very rarely in patients treated with factor IX containing products. In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see section "Special warnings and precautions for use").
If allergic-anaphylactic reactions occur, the administration of Beriplex P/N 500 has to be discontinued immediately (e.g. discontinue injection) and an appropriate treatment has to be initiated (see section "Special warnings and precautions for use").
Development of antibodies to one or several factors of the prothrombin complex may occur in very rare cases. 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.
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).
For safety with regard to transmissible agents, see section "Special warnings and precautions for use".

STORAGE AND STABILITY
Do not store above 25 °C. Do not freeze.
Keep the vial in the outer carton, in order to protect from light.
Beriplex P/N 500 must not be used after the expiry date given on the pack and container.
After reconstitution, from a microbiological point of view and as Beriplex P/N 500 contains no preservative, the reconstituted product should be used immediately. The physico-chemical stability has been demonstrated for 24 hours at room temperature (max. 25 °C). However, if it is not administered immediately, storage shall not exceed 8 hours at room temperature.
Any unused product or waste material should be disposed of in accordance with local requirements.

Keep out of the reach and sight of children.

DATE OF LAST REVISION
July 2011