



Package leaflet: Information for the user

Beriplex® P/N 250, 500 and 1000 IU

Powder and solvent for solution for injection
Human prothrombin complex

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Beriplex is and what it is used for
2. What you need to know before you use Beriplex
3. How to use Beriplex
4. Possible side effects
5. How to store Beriplex
6. Contents of the pack and further information

1. What Beriplex is and what it is used for

What is Beriplex?

Beriplex is presented as powder and solvent. It is a white or slightly coloured powder or friable solid. The made up solution is to be given by injection into a vein. Beriplex is made from human plasma (this is the liquid part of the blood) and it contains the human coagulation factors II, VII, IX and X. Concentrates including these coagulation factors are called prothrombin complex products. The coagulation factors II, VII, IX and X are vitamin K-dependent and are important for blood clotting (coagulation). Lack of any of these factors means that blood does not clot as quickly as it should and so there is an increased tendency to bleed. The replacement of factors II, VII, IX and X with Beriplex will repair the coagulation mechanisms.

What is Beriplex used for?

Beriplex is used for the prevention (during surgery) and treatment of bleedings caused by the acquired or congenital lack of vitamin K-dependent coagulation factors II, VII, IX and X in the blood, when purified specific coagulation factor products are not available.

2. What you need to know before you use Beriplex

The following sections contain information that your doctor should consider before you are given Beriplex.

Do NOT use Beriplex:

- if you are allergic to any of the active substances or other ingredients of this medicine (listed in section 6).

Please inform your doctor if you are allergic to any medicine or food.

- if you are more likely to suffer from blood clots than normal (patients at risk of disseminated intravascular coagulation)
- if you show an allergic response to heparin, causing a fall in the number of blood platelets (heparin-induced thrombocytopenia Type II, HIT Type II).

Please inform your doctor or pharmacist if you suffer from such a disease.

Warnings and precautions

Talk to your doctor or pharmacist before using Beriplex in case of:

- Acquired deficiency of the vitamin K-dependent coagulation factors: This may be induced by treatment with medicines inhibiting the vitamin K effect. Beriplex is only allowed to be used when rapid correction of the prothrombin complex levels is necessary, e.g. in case of major bleedings or emergency surgery
- Congenital deficiency of any of the vitamin K-dependent factors: In this case you should use specific coagulation factor products when available
- Allergic or anaphylactic-type reactions (a serious allergic reaction that causes severe difficulty in breathing or dizziness):

The application of Beriplex should be stopped immediately (e.g. discontinue injection)

- Increased risk of formation of blood clots in a blood vessel (thrombosis), particularly:
 - if you have had a heart attack (a history of coronary heart disease or myocardial infarction)
 - if you suffer from liver disease
 - if you have just had surgery (patients per- or postoperatively)
 - in new-born infants (neonates)
 - if you are more likely to suffer from blood clots than normal (patients at risk of thromboembolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency)
- Increased coagulation risk due to increased consumption of blood platelets or blood coagulation factors. Treatment with Beriplex can only be started after treatment of the underlying cause.
- Reduced development of blood platelets due to heparin (heparin-induced thrombocytopenia, HIT Type II). Heparin, a protein with a blood clot dissolving effect, is an ingredient of Beriplex. The severe form of a decrease in blood platelets may be associated with
 - blood clots in the vein or leg,
 - an increased formation of blood clots,
 - in some cases with skin rash where the injection was given,
 - pinpoint-sized haemorrhages and
 - tarry stool.

In these cases the effect of heparin may be diminished (heparin tolerance).

If these symptoms occur, you should stop using the product immediately and contact your doctor. In the future no heparin-containing products should be used.

- A special form of inflammation of the kidneys has been reported after treatment of patients who suffer from haemophilia B with factor IX inhibitors. These patients were also known to have a history of allergic reaction.

Your doctor will consider carefully the benefit of treatment with Beriplex compared with the risk of these complications.

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,
- the inclusion of 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), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived prothrombin complex products.

It is strongly recommended that every time you receive a dose of Beriplex, the name and batch number of the medicine are recorded in order to maintain a record of the batched used.



mit Perforation

The following information is intended for healthcare professionals only:

Qualitative and quantitative composition

Beriplex 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)	Beriplex P/N 1000 content per vial (IU)
Active Ingredients				
Human coagulation factor II	20 – 48	200 – 480	400 – 960	800 – 1920
Human coagulation factor VII	10 – 25	100 – 250	200 – 500	400 – 1000
Human coagulation factor IX	20 – 31	200 – 310	400 – 620	800 – 1240
Human coagulation factor X	22 – 60	220 – 600	440 – 1200	880 – 2400
Further active ingredients				
Protein C	15 – 45	150 – 450	300 – 900	600 – 1800
Protein S	12 – 38	120 – 380	240 – 760	480 – 1520

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.

Posology and method of administration

Posology

Only general dosage guidelines are given below.

The amount and the frequency of administration depends on the indication for treatment and 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).

- 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 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 antagonists treatment is not supported by clinical data and therefore not recommended.

- 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 1.9 % (0.019 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 0.019 IU/ml.

The required dosage is determined using the following formula:

Required units = body weight [kg] x desired factor X rise [IU/ml] x 53

where 53 (ml/kg) is the reciprocal of the estimated recovery.

Note that the calculation is based upon data from patients receiving vitamin K antagonists. A calculation based upon data from healthy subjects would provide a lower estimate of the required dose.

If the individual recovery is known, that value should be used for calculation.

Product specific information is available from clinical studies in healthy volunteers (N = 15), in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleeding (N = 98, N = 43).

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.

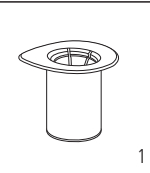
Method of administration

General instructions

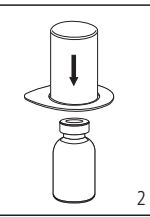
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.
- Reconstitution and withdrawal must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

Reconstitution

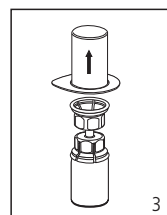
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.



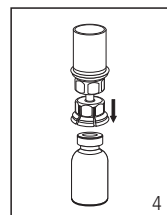
1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!



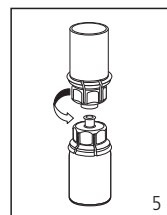
2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adaptor end **straight down** through the solvent vial stopper.



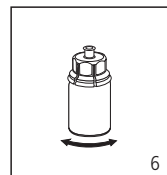
3. Carefully remove the blister package from the Mix2Vial set by holding at the rim and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.



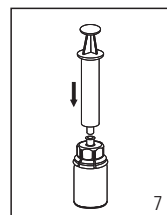
4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adaptor end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.



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. Discard the solvent vial with the blue Mix2Vial adaptor attached.

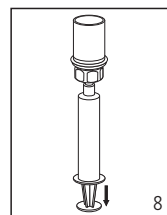


6. Gently swirl the product vial with the transparent adaptor attached until the substance is fully dissolved. Do not shake.

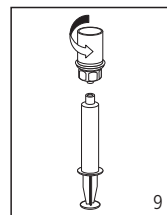


7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application



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. 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 adaptor 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 intravenously (not more than 8 ml/min*).

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

Special warnings and precautions for use

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

Notes for control of platelet count:

Platelet count should be closely monitored.

Interaction with other medicinal products and other forms of interaction

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.

* in Beriplex clinical trials patients weighing <70 kg were instructed to be dosed with a maximum infusion speed of 0.12 ml/kg/min (less than 8 ml/min)



Other medicines and Beriplex

- Tell your doctor or pharmacist if you are taking, have recently taken or might take any medicines.
- Beriplex may inhibit the effect of vitamin K antagonist treatment. No interactions with other medicinal products are known.
- This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.

Pregnancy, breast-feeding and fertility

- If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.
- During pregnancy and breast-feeding Beriplex should be given only if it is clearly indicated.
- No fertility data are available.

Driving and using machines

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

Beriplex contains sodium

Beriplex contains up to 343 mg sodium (approximately 15 mmol) per 100 ml. Please take this into account if you are on a controlled sodium diet.

3. How to use Beriplex

Treatment should be started and supervised by a physician who is experienced in this type of disorder.

Dosage

The amount of Factor II, VII, IX and X you need will depend on several factors, such as your body weight, the severity and nature of your disease, the site and intensity of the bleeding or the need to prevent bleeding during an operation or investigation (see section "The following information is intended for healthcare professionals only").

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Overdose

Your doctor should regularly check your blood clot status during the treatment. High doses of prothrombin complex concentrate have been associated with instances of heart attack, disseminated intravascular coagulation and an increased formation of blood clots in a blood vessel in patients at risk of these complications.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been observed **commonly** (may affect up to 1 in 10 people):

- There is a risk of formation of blood clots (see section 2)
- Headache
- Increase in body temperature

The following side effects occurred **uncommonly** (may affect up to 1 in 100 people):

- Hypersensitivity or allergic reactions (see section 2)

The frequency of the following side effects is **not known** (cannot be estimated from the available data)

- Excessive coagulation resulting in severe bleeding
- Anaphylactic reactions including shock (see section 2)
- Formation of circulating antibodies inhibiting one or more coagulation factors

Paediatric population

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

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

UK:

Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

Ireland:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
Email: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Beriplex

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the label and carton.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.
- Beriplex does not contain a preservative, so the made-up solution should preferably be used immediately.

6. Contents of the pack and other information

What Beriplex contains:

Beriplex 250 IU contains 200 – 310 IU human coagulation factor IX per vial.
Beriplex 500 IU contains 400 – 620 IU human coagulation factor IX per vial.
Beriplex 1000 IU contains 800 – 1240 IU human coagulation factor IX per vial.

The active substance is:

A concentrate of the human coagulation factors II, VII, IX and X, Proteins C and S

The other ingredients are:

Human antithrombin III, heparin, human albumin, sodium chloride, sodium citrate, HCl or NaOH (in small amounts for pH adjustment)

Solvent: Water for injections

What Beriplex looks like and contents of the pack

Beriplex is presented as a white or slightly coloured powder and is supplied with water for injections as solvent. The powder should be dissolved with 10 ml (250 IU), 20 ml (500 IU) or 40 ml (1000 IU) of water for injections.

The made-up solution should be clear or slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.

Presentation

One pack with 250 IU containing:

- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20

One pack with 500 IU containing:

- 1 vial with powder
- 1 vial with 20 ml water for injections
- 1 filter transfer device 20/20

One pack with 1000 IU containing:

- 1 vial with powder
- 1 vial with 40 ml water for injections
- 1 filter transfer device 20/20

Marketing Authorisation Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

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