

**EU-SUMMARY OF PRODUCT CHARACTERISTICS –
EDS/EU/ENGLISH)**

BERIPLAST P COMBI-SET

Rev.: **22-JUL-2008** / completion of EU-renewal (R02)

Supersedes previous versions

Rev.: 08-MAY-2008 / renewal/ day 60 comments FR + AT

Rev.: 02-MAR-2007 / CSL Behring

1. NAME OF THE MEDICINAL PRODUCT

Beriplast P 0.5 ml, 1 ml, 3 ml, powders and solvents for sealant
Combi-Set

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative composition

Combi-Set I:

Active ingredients

Human fibrinogen, Coagulation Factor XIII (human), Aprotinin (bovine)

Combi-Set II:

Active ingredients

Human thrombin, Calcium Chloride

Quantitative composition

Combi-Set I	per 1 ml
<u>Vial 1 Fibrinogen Concentrate:</u>	
total dried substance	174 mg
<i>fibrinogen</i> (human plasma protein fraction)	90 mg
<i>coagulation factor XIII</i> (human plasma protein fraction)	60 U*
<u>Vial 2 Aprotinin Solution:</u>	
volume	1.0 ml
bovine lung <i>aprotinin</i>	1000 KIU**
corresponding to	0.56 PEU***
* 1 Unit (U) corresponds to the Factor XIII activity of 1 ml fresh citrated plasma (pooled plasma of healthy donors).	
** KIU = Kallikrein Inactivator Unit	
*** PEU = Ph. Eur. Unit (1 PEU $\hat{=}$ 1800 KIU)	
Combi-Set II	per 1 ml
<u>Vial 3 Thrombin:</u>	
total dried substance	7.6 mg
with a human plasma protein fraction <i>thrombin</i> activity	500 IU
<u>Vial 4 Calcium Chloride Solution:</u>	
volume	1.0 ml
<i>calcium chloride dihydrate</i>	5.9 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powders and solvents for sealant.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Beriplast P can be used locally as supportive treatment where standard surgical techniques are insufficient

- For improvement of haemostasis (including endoscopic treatment of bleeding gastroduodenal ulcer)
- As a tissue to promote adhesion/sealing or as suture support

4.2 Posology and method of administration

The use of Beriplast P is restricted to experienced physicians.

Posology

The volume of Beriplast P to be administered and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose of Beriplast P to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of Beriplast P must be individualised by the treating physician. In clinical trials, the individual dosages of Beriplast P have typically ranged from 0.5 to 4 ml. For some procedures (e.g., liver traumata, or the sealing of large burned surfaces) larger volumes (10 ml or more) may be required.

The initial volume of Beriplast P to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

Method and route of administration

For epilesional use.

Prepare the solutions as described in section 6.6 “Special precautions for disposal and other handling”.

The reconstituted solutions (of vial 1 and 3) are to be administered locally to the tissue (sequentially or in combination). Unlike other haemostatic agents that must be removed once haemostasis is achieved, Beriplast P remains in place after application and is degraded by the normal physiological process of clot lysis.

Before Beriplast P is applied, the surface of the wound should be as dry as possible. See section 6.6 for more detailed instructions.

4.3 Contraindications

Beriplast P must not be applied intravascularly.

Arterial and strong venous bleeding.

Known hypersensitivity to bovine proteins or to any other components of the product.

4.4 Special warnings and precautions for use

Beriplast P may only be used for epilesional administration. Beriplast P must not be applied intravascularly!

Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

If allergic or anaphylactic reactions occur, the administration of Beriplast P has to be discontinued immediately and an appropriate treatment has to be initiated. Therapeutic measures depend on the nature and severity of the event. The current medical standards for shock treatment are to be observed.

Beriplast P contains bovine protein (aprotinin). Even in case of strict local application, there is a risk of anaphylactic reactions, linked to the presence of bovine aprotinin. The risk seems higher in case of previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin-containing products should be documented in the patients' records.

Care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

Special note on local injection:

Administration of Beriplast P in the endoscopic treatment of gastrointestinal bleedings can cause tissue damage, which can lead to formation of intramural haematoma. Abdominal pain, nausea, or vomiting within 1 to 3 days after such endoscopic treatment can constitute symptoms of intramural haematoma. In patients with intramural haematoma of the duodenal wall, pancreatitis has been reported in single literature cases. Therefore, differential diagnosis for pancreatitis should be carefully evaluated.

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 infections 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 HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. haemolytic anaemia).

It is strongly recommended that every time that Beriplast P 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 Interactions with other medicinal products and other forms of interactions

No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, Beriplast P may be denatured after exposure with solutions containing alcohol, iodine or heavy metals (e.g., antiseptic solutions). Such substances should be removed to the greatest possible extent before applying Beriplast P.

4.6 Pregnancy and lactation

The safety of Beriplast P for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development.

Only limited experience regarding the administration of Beriplast P in pregnant women is available. Therefore, the product should be administered to pregnant and lactating women only if clearly indicated.

4.7 Effects on ability to drive and use machines

Not applicable (as there is no systemic use).

4.8 Undesirable effects

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)

Immune system disorders

In very rare cases, hypersensitivity or allergic reactions (e.g., dyspnoea, flush/rash, urticaria, hypotension, bronchospasm) may occur, extending in isolated cases as far as anaphylactic shock. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to bovine proteins or other constituents of the product.

For safety with respect to transmissible agents see section 4.4 subheading “Virus safety”.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local hemostatics, ATC code: B02BC

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both, the conversion of fibrinogen and the crosslinkage of fibrin. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

5.2 Pharmacokinetic properties

Beriplast P is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Beriplast P is metabolized in the same way as is endogenous fibrin by fibrinolysis and phagocytosis.

Beriplast P is only applied locally and thus immediately available.

5.3 Preclinical safety data

Single dose toxicity data reveal no special hazard for humans, beyond the information included in other parts of the SPC. Due to its nature as well as its special method of application no genotoxicity and cancerogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Combi-Set I

Vial 1: powder

human albumin, L-arginine hydrochloride, L-isoleucine, sodium chloride, sodium citrate dihydrate, sodium L-glutamate monohydrate

Vial 2: solvent

sodium chloride, water for injections

Combi-Set II

Vial 3: powder

sodium chloride, sodium citrate-dihydrate

Vial 4: solvent

water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with medicinal products other than the appropriate solvents mentioned in section 6.6, subheading "Presentations".

6.3 Shelf life

2 years

After reconstitution the physico-chemical stability has been demonstrated for 24 hours at room temperature (up to max. +25 °C), if stored in the unopened sterile blister packaging. If stored outside the sterile blister packaging, from a microbiological point of view and as Beriplast P contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours at room temperature.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze. Keep container in the outer carton. For storage conditions of the reconstituted medicinal product, see section 6.3 "Shelf life".

6.5 Nature and contents of container

Immediate containers

Injection vials:

Colourless glass,

- Type I acc. to Ph. Eur. in case of Fibrinogen Concentrate 0.5 and 1 ml, Aprotinin Solution, Thrombin and Calcium Chloride Solution
- Type II acc. to Ph. Eur. in case of Fibrinogen Concentrate 3 ml each sealed with rubber stopper and aluminium cap.

Presentations

Pack for Beriplast P 0.5 ml

Combi-Set I for preparing the fibrinogen solution, consisting of vials 1 and 2 linked together via a transfer device:

- Vial 1 containing powder of fibrinogen and coagulation factor XIII
- Vial 2 containing aprotinin solution

Combi-Set II for preparing the thrombin solution, consisting of vials 3 and 4 linked together via a transfer device:

- Vial 3 containing thrombin powder
- Vial 4 containing calcium chloride solution

Application set, consisting of:

- 2 sterile disposable tuberculin syringes
- Pantaject application kit
- 2 sterile disposable spray-tips
- 4 sterile disposable cannulas

Pack for Beriplast P 1 ml

Combi-Set I for preparing the fibrinogen solution, consisting of vials 1 and 2 linked together via a transfer device:

- Vial 1 containing powder of fibrinogen and coagulation factor XIII
- Vial 2 containing aprotinin solution

Combi-Set II for preparing the thrombin solution, consisting of vials 3 and 4 linked together via a transfer device:

- Vial 3 containing thrombin powder
- Vial 4 containing calcium chloride solution

Application set, consisting of:

- 2 sterile disposable tuberculin syringes
- Pantaject application kit
- 2 sterile disposable spray-tips
- 4 sterile disposable cannulas

Pack for Beriplast P 3 ml

Combi-Set I for preparing the fibrinogen solution, consisting of vials 1 and 2 linked together via a transfer device:

- Vial 1 containing powder of fibrinogen and coagulation factor XIII
- Vial 2 containing aprotinin solution

Combi-Set II for preparing the thrombin solution, consisting of vials 3 and 4 linked together via a transfer device:

- Vial 3 containing thrombin powder
- Vial 4 containing calcium chloride solution

Application set, consisting of:

- 2 sterile disposable 3 ml syringes
- Pantaject application kit
- 3 sterile disposable spray-tips
- 4 sterile disposable cannulas

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Beriplast P must not be used after the expiry date given on the pack and container.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted solutions should be inspected visually for particulate matter and discoloration prior to administration.

Preparation and withdrawal of the solutions

(see Figures 1 to 4 in the lid of the outer carton):

- Bring Beriplast P to room temperature (not exceeding +25 °C).
- Take the cardboard stand (containing Combi-Sets I and II) out of the outer carton and place in a vertical position.
- Do not open the sterile blister packaging and leave the Combi-Sets I and II in the cardboard stand.
- Reconstitute each set separately.
- Apply strong pressure to the top of the upright Combi-Sets in order to transfer the solvents from the solvent vial (2 resp. 4) into the vial with the powder (1 resp. 3).
- The solvent is drawn in by vacuum via the transfer device (see Fig. 1).
- Afterwards leave to stand at room temperature. The process of reconstitution is complete after five to ten minutes at the latest. A clear to slightly opalescent solution is obtained. Air-bubbles may make the viscous solution appear turbid but such turbidity does not interfere with the efficacy or usability of the product.
- Note the date and time of reconstitution in the empty space on the cardboard stand (space on right side).
- Ensure that Combi-Sets I and II are stored in an upright position once reconstituted.

- Prior to use tear open the sterile blister packaging (see Fig. 2) and remove Combi-Set I and II under sterile conditions. Disconnect the empty vials (2 resp. 4) plus transfer devices (see Fig. 3).
- Incline Vial 1 (fibrinogen solution/blue marking) and draw up the contents into the blue marked syringe. Completely draw up the contents of Vial 3 (thrombin solution/red marking) into the red marked syringe (see Fig. 4).

Use the reconstituted solutions immediately after withdrawal into the syringes. Any unused solution or waste material should be disposed of in accordance with local requirements.

Application

Before Beriplast P is applied, the surface of the wound should be as dry as possible.

Separate application of fibrinogen solution and thrombin solution:

- a) Apply the fibrinogen solution to the tissue site requiring adhesion and immediately overlay with the thrombin-containing solution.
- b) The tissues requiring adhesion should be fixed in place for several minutes until provisional adhesion is achieved.

Joint application with Pantaject[®] application kit:

For joint application of fibrinogen solution and thrombin solution, the application kit can be used.

Handling of the application kit for Beriplast P (see diagram on the application kit):

Remove the needles from the syringes filled with the fibrinogen solution (blue marking) and thrombin solution (red marking).

- (A) Insert the Y-piece (3) in the conical recess of the syringe holder (4).
- (B) Firmly connect to the Y-piece (3) the syringes filled with the fibrinogen solution (1/blue marking) and thrombin solution (2/red marking).
- (C) Snap both syringes into the syringe holder (4).
- (D) Connect the grip plate (5) to the syringe plungers to prevent jamming of the syringe plungers and to ensure smooth forward movement.
- (E) Finally firmly screw on the spray tip (6) or the application cannula (7) (both equipped with a Luer-Lock connector).

For covering large wound surfaces the fibrin sealant can be sprayed using the enclosed spray-tips, or used in combination with fleece consisting of e.g. polyglycolic acid or collagen.

Before use in the wound region the system must be checked for blockages. Never push the syringe plungers against a resistance! Any interruption in the application, even of short duration, results in blockage of both either the spray tip or application cannula. In such cases the spray tip or application cannula is unsuitable for further use and must be replaced. For this purpose the 0.5 and 1 ml Beriplast P packages contain two spray tips and the 3 ml packages contain three spray tips; each package contains four blunt application cannulas.

By applying an even pressure to the grip plate – like for an injection – the fibrin sealant is sprayed from the spray tip as a fine, even aerosol. The best distance is about 10 cm. A fine film of fibrin sealant forms on the tissue to be coated.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

– country specific –

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

– country specific –

10. DATE OF REVISION OF THE TEXT

July 2008