

EU PACKAGE INSERT – (PI/EU/ENGLISH)

BERIPLAST P COMBI-SET 1 ml

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Supersedes previous versions

Rev.: 15-JUL-2008 / day 85 comments AT

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PACKAGE LEAFLET : INFORMATION FOR THE USER

Beriplast P 1 ml, powders and solvents for sealant
Combi-Set I: Human fibrinogen, Coagulation Factor XIII (human), Aprotinin (bovine)
Combi-Set II: Human thrombin, Calcium Chloride

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and should not be passed 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.

In this leaflet:

1. What Beriplast P 1 ml is and what it is used for
2. Before you are given Beriplast P 1 ml
3. How to use Beriplast P 1 ml
4. Possible side effects
5. How to store Beriplast P 1 ml
6. Further information

1. WHAT BERIPLAST P 1 ml IS AND WHAT IT IS USED FOR

What is Beriplast P 1 ml?

Beriplast P 1 ml is presented as powder and solvent. The made up solutions are to be given epilesionally.

Beriplast P 1 ml contains fibrinogen and thrombin and initiates the last phase of physiological blood coagulation.

What is Beriplast P 1 ml used for?

Beriplast P 1 ml can be used locally as supportive treatment where standard techniques are insufficient

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

2. BEFORE YOU ARE GIVEN BERIPLAST P 1 ml

The following sections contain information that your doctor should consider before you are given Beriplast P 1 ml.

Do NOT use Beriplast P 1 ml:

- intravascularly
- in case of arterial and strong venous bleeding
- in case of known hypersensitivity to bovine proteins or to any other components of the product.

Take special care with Beriplast P 1 ml:

Beriplast P 1 ml may only be used for epilesional administration. Beriplast P 1 ml 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 1 ml has to be discontinued immediately and an appropriate treatment has to be initiated. Therapeutic measures depend on the nature and severity of the side effect. The current medical standards for shock treatment are to be observed.

Beriplast P 1 ml 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.

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 and hepatitis C virus (inflammation of the liver).

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A (inflammation of the liver) and 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).

It is strongly recommended that every time that Beriplast P 1 ml 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.

Taking other medicines

- No formal interaction studies have been performed.
- Similar to comparable products or thrombin solutions, Beriplast P 1 ml 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 1 ml.
- This medicinal product must not be mixed with medicinal products other than the appropriate solvents (see “Pharmaceutical form and presentation”, subheading “Presentation”).

Pregnancy and breast-feeding

The safety of Beriplast P 1 ml 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 1 ml in pregnant women is available. Therefore, the product should be administered to pregnant and lactating women only if clearly indicated.

Driving and using machines

Not applicable (as there is no systemic use).

3. HOW TO USE BERIPLAST P 1 ml

The use of Beriplast P 1 ml is restricted to experienced physicians.

Dosage

The volume of Beriplast P 1 ml to be administered and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

Overdose

No case of overdose has been reported.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Beriplast P 1 ml can cause side effects, although not everybody gets them.

The following side effects have been observed very rarely (less than 1 of 10,000 patients)

Immune system disorders

Hypersensitivity or allergic reactions (e.g., dyspnoea, flush/rash, urticaria, hypotension, bronchospasm), 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.

5. HOW TO STORE BERIPLAST P 1 ml

Beriplast P 1 ml must not be used after the expiry date given on the pack and container.

- Store in a refrigerator at 2 °C - 8 °C.
- Do not freeze.
- Keep container in the outer carton.
- 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 1 ml 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.
- Any unused solution or waste material should be disposed of in accordance with local requirements.
- **Keep out of the reach and sight of children!**

6. FURTHER INFORMATION

What Beriplast P 1 ml contains

The active substances are:

Combi-Set I	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 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 \square 1800 KIU)

Combi-Set II	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 ml
<i>calcium chloride dihydrate</i>	5.9 mg

The other ingredients are:

Human albumin, L-arginine hydrochloride, L-isoleucine, sodium chloride, sodium citrate dihydrate, sodium L-glutamate monohydrate, water for injections

What Beriplast P 1 ml looks like and contents of the pack

Beriplast P 1 ml is presented as powders and solutions. The made-up solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted solutions should be inspected visually for particulate matters and discoloration prior to administration.

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

Marketing Authorisation Holder and Manufacturer

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

This medicinal product is authorised in the Member States of the EEA under the following names:

Beriplast 0.5 ml/1 ml/3 ml	France
Beriplast P	Greece, Italy, Netherlands, Poland
Beriplast P Combi-Set	Romania, Slovakia, Slovenia, Spain
Beriplast P Combi-Set Fibrinkleber-Set	Austria
Beriplast P Combi-Set 0,5ml/1 ml/3 ml	Germany
Beriplast P Combi-Set 1 ml/3 ml fibrin sealant set	Hungary

This leaflet was last approved in July 2008

The following information is intended for medical or healthcare professionals only

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special note on local injection:

Administration of Beriplast P 1 ml 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.

POSODOLOGY AND METHOD OF ADMINISTRATION

Posology

The dose of Beriplast P 1 ml to be applied is governed by variables including, but not limited to the type of surgical intervention, the size of the area of intended application, and the number of applications.

Application of Beriplast P 1 ml must be individualised by the treating physician. In clinical trials, the individual dosages of Beriplast P 1 ml 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 1 ml 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 of administration

For epilesional use only

A. Preparation and withdrawal of the solutions

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

- Bring Beriplast P 1 ml 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.

B. Application

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 1 ml remains in place after application and is degraded by the normal physiological process of clot lysis.

Before Beriplast P 1 ml 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 1 ml (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 1 ml Beriplast P packages contain two spray tips and 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.