

COMPANY core Package Insert

Beriplast® P Combi-Set 1 ml

Fibrin Sealant Set

Qualitative and quantitative composition

Qualitative composition

Combi-Set I:

Active ingredients:

Fibrinogen (human), Coagulation factor XIII (human), aprotinin (bovine)

Combi-Set II:

Active ingredients:

Thrombin (human), Calcium chloride

Quantitative composition:

The Beriplast P 1 ml Set contains:

Combi-Set I	1 ml
Vial 1 Fibrinogen Concentrate:	
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*
human albumin, L-arginine hydrochloride, L-isoleucine, sodium chloride, sodium citrate dihydrate, sodium L-glutamate monohydrate	
Vial 2 Aprotinin Solution:	
Volume	1.0 ml
bovine lung <i>aprotinin</i>	1000 KIU**
corresponding to	0.56 PEU***
sodium chloride, water for injections	
* 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 ≡ 1800 KIU)	
Combi-Set II	1 ml
Vial 3 Thrombin:	
total dried substance	7.6 mg
with a human plasma protein fraction <i>thrombin</i> activity	500 IU
sodium chloride, sodium citrate dihydrate	
Vial 4 Calcium Chloride Solution:	
Volume	1.0 ml
<i>calcium chloride dihydrate</i>	5.9 mg
water for injections	

Pharmaceutical form and presentation

Pharmaceutical form

Powders (vials 1 and 3) and solvents (vials 2 and 4) for sealant.

Presentation

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 dry substance 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 dry substance of thrombin
- Vial 4 containing calcium chloride solution

Application kit, consisting of:

- 2 sterile disposable tuberculin syringes
- Y-piece
- syringe holder
- grip plate
- 2 sterile disposable spray-tips
- 2 sterile disposable application cannulas

Pharmaco-therapeutic group

Haemostyptics/antihaemorrhagics

Name and address of the marketing authorization holder

ZLB Behring AG
Emil-von-Behring-Str. 76
P.O. Box 1230
D-35002 Marburg
Germany

Therapeutic indications

Beriplast P 1 ml can be used locally as supportive treatment in external surgical disciplines, (not internal tissues) to achieve

- tissue adhesion / sealing,

- suture support

For tooth extraction in patients with hereditary clotting factor deficiency (e.g. hemophilia)

Contra-indications

Arterial and strong venous bleeding.

Known hypersensitivity to bovine proteins or other constituents of the product.

Pregnancy and lactation

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.

Special warnings and special precautions for use

Beriplast P 1 ml may only be used for local administration. Beriplast P 1 ml must not be applied intravascularly! Thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

If allergic or anaphylactic reactions occur, the administration 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 (see also "Undesirable effects").

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:

As with each injection, tissue damage is possible independent from the product.

Virus safety:

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature.

Some viruses, such as parvovirus B 19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B 19 may most seriously affect seronegative pregnant women, or immune-compromised individuals.

To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of donors and donations. In addition, virus removal and/or inactivation procedures are included in the production process of Beriplast P 1 ml:

- Beriplast P 1 ml is prepared exclusively from plasma donations which have been tested negative for antibodies to HIV-1, HIV-2, HCV and for HBs antigen. The levels of ALT (GPT) in the plasma are also determined and must not exceed twice the normal value specified in the test.
- In addition, the plasma pool is tested for antibodies to HIV-1, HIV-2, HCV and for HBs antigen. The plasma pool is used for further processing only if the results are negative.
- The production process of Beriplast P 1 ml contains various steps which contribute towards the elimination/inactivation of viruses. The heat-treatment of the preparation in aqueous solution at 60°C for 10 hours was introduced for virus inactivation.

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 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.

Incompatibilities

Beriplast P 1 ml should not be mixed with other medicinal products than the appropriate solvents.

Dosage and administration

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.

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.

The initial volume of Beriplast P 1 ml to be applied at a target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

Overdose:

There is no experience of overdosage.

Administration

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 out of the outer carton (containing Combi-Sets I and II 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 lyophilizate vial (1 resp. 3).
- The solvent is drawn into the vacuum via the transfer device (see Fig. 1).
- Afterwards leave to stand at room temperature. The process of reconstitution is complete after one to two minutes. Air-bubbles may make the viscous solution appear turbid but such turbidity does not interfere.
- 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 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).

B. Application:

The reconstituted solutions (of vial 1 and 3) are to be administered locally to the tissue (sequentially or in combination). 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.

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 collagen fleece.

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 two 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 - 20 cm. A fine film of fibrin sealant forms on the tissue to be coated.

Undesirable effects

In 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.

If allergic or anaphylactic reactions occur, the administration has to be discontinued immediately and an appropriate treatment has to be initiated. The current medical standards for shock treatment are to be observed.

As necessary, additional treatment should be given as follows:

- a) Mild reactions: Administer corticosteroids and antihistamines.
- b) Severe or life-threatening reactions (e.g. anaphylactic shock), depending on the severity of the reaction:
 - Immediately inject adrenaline slowly i.v.,
 - Plus high doses of corticosteroids slowly i.v.,
 - If necessary, administer volume replacement and/or oxygen.

Storage and stability

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

Beriplast P 1 ml is to be stored protected from light at a refrigerated temperature of +2 to +8°C.

Use the reconstituted solutions immediately after withdrawal into the syringes.

The storage conditions for the finished product and the reconstituted solutions should be observed strictly.

Keep out of the reach of children!

Once reconstituted the thrombin and fibrinogen solutions remain stable in the vials at +15 to +25°C for 8 hours if stored outside the sterile blister packaging.

Any unused solution must be discarded appropriately.

Date of last revision

December 2000

Additional information

Other presentations

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 dry substance 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 dry substance of thrombin
- Vial 4 containing calcium chloride solution

Application kit, consisting of:

- 2 sterile disposable 3 ml syringes
- Y-piece
- syringe holder
- grip plate
- 3 sterile disposable spray-tips
- 2 sterile disposable application cannulas

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר.

The Ministry of health has determined the format of this leaflet and its content has been examined and approved.

Manufacturer: ZLB Behring AG, Marburg, Germany.

Manufacturer's agent: Mediline Ltd., 22 Ben Gurion St., Herzliya 46785.

Importer: Mediline Ltd., P.O.Box 531 Yokneam 20692.

I 01211204