

A Nurse's Guide to Fibrin Sealants – Your Questions Answered

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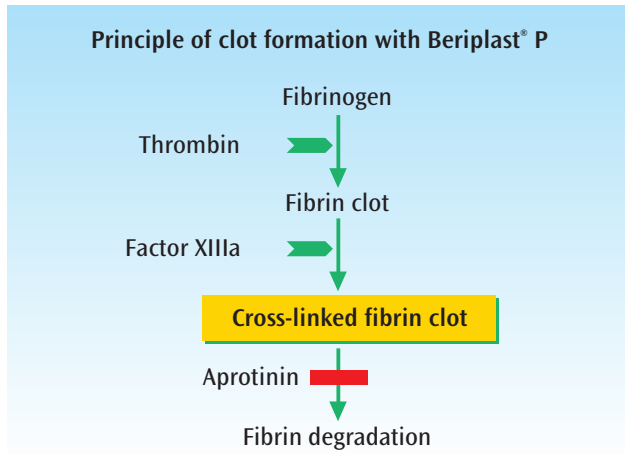
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Fibrin sealants and their uses

What are fibrin sealants and how are they used?

Fibrin sealants:

- are surgical haemostatic and adhesive agents derived mainly from plasma products
- contain fibrinogen, thrombin, factor XIII, an anti-fibrinolytic agent (such as aprotinin), and calcium chloride
- reproduce the final steps in the coagulation cascade, forming a stable fibrin clot, arresting blood loss and assisting the normal healing process
- form blood clots that are similar to normal clots and which, like normal clots, are degraded naturally by the body's enzymes.



Fibrin sealants are used mainly for haemostasis, suture support or adhesion of tissues.¹ For example they are used:

- to assist in achieving haemostasis in a bleeding field – particularly in situations where sutures or clips are not appropriate
- to reduce the blood flow from solid organs
- to help seal anastomoses or leaks from hollow organs
- to assist or replace sutures in surgical procedures, particularly where suturing is difficult or impossible.

Fibrin sealants can be used in a range of surgical procedures, including:

- cardiovascular surgery²
- thoracic surgery³
- vascular surgery²
- abdominal surgery^{4,5}
- neurosurgery⁶⁻⁹

Fibrin sealants **form a stable clot, arresting blood loss and promoting wound healing**. They contain **fibrinogen, thrombin**, different quantities of **factor XIII**, an anti-fibrinolytic agent (such as **aprotinin**), and **calcium chloride**.

Fibrin sealants and their uses

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What are the clinical advantages of fibrin sealants?

Fibrin sealants can reduce complications in surgery, such as haemorrhage and dehiscence, reduce operating times and reduce the need for further operations resulting from post-operative bleeding complications. The length of hospital stays can be significantly reduced as a result.

Fibrin sealants also:

- aid wound closure in parenchymal tissue (lungs, liver, pancreas and spleen)^{10–12}
- reduce fluid secretions and the need for chest drain, and the incidence of complications such as pneumothorax in thoracic surgery¹
- result in haemostasis in patients with bleeding ulcers¹³
- result in rapid haemostasis, fewer sutures and shorter operating times in vascular and microvascular surgery²
- reduce the incidence of infection, cerebrospinal fluid leakage and fistulae in neurosurgical procedures^{6–9}

Fibrin sealants **promote haemostasis** in surgical procedures, **supplement sutures** and **reduce postoperative complications**.

Are fibrin sealants safe?

Fibrin sealants have been used for over 20 years. They are generally associated with good tolerability across a variety of applications. As they contain human plasma products, modern, commercially-available fibrin sealants undergo a variety of purification processes to reduce the risk of transmission of blood-borne infectious agents to the patient. The degree of purification varies from one product to another.

Are all fibrin sealants the same?

Whilst the composition of all fibrin sealants is essentially the same, different formulations mean that the ease of preparation, storage and use of fibrin sealants can vary considerably. For example, some preparations need to be stored in a freezer; therefore defrosting is necessary before use. Other sealants require heating to mix the components adequately before use.

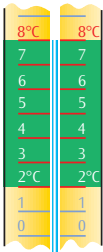
Storage and preparation

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How should Beriplast® P be stored?

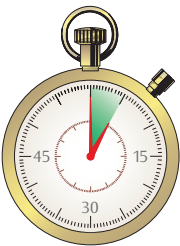
Beriplast® P should be refrigerated at 2–8°C. Storage at below 10°C is recommended in Japan.

How long after removal from refrigeration can Beriplast® P be used?



Regulatory approval is for storage of Beriplast® P at 2–8°C. However, boxed and non-reconstituted Beriplast® P can be stored at room temperature for up to one week (Data on File, Aventis Behring)¹⁴. Several users report that they prefer to remove Beriplast® P from the refrigerated storage at night before they wish to use it. Other Beriplast® P users remove up to one week's supply from refrigerated storage. It is important to note that Beriplast® P must be used within its shelf life.

How long does Beriplast® P take to reach room temperature after it has been taken out of refrigeration?



1 mL Beriplast® P reaches room temperature within about 5 minutes of removal from refrigeration; the larger 3 mL vial may take up to 30 minutes, but this process can be accelerated by:

- removing the product from the cardboard box (which otherwise acts as an insulator)
- manually rolling the plasma component vials – still inside the sterile pouch – in the palms of one's hands. Take care not to shake the contents and to keep the liquid component above the powder at all times.

Preparation of Beriplast® P does not require any special heating devices.

Storage and preparation

How long does it take to prepare Beriplast® P for use?

Once at room temperature, experienced nurses say it takes less than 4 minutes to prepare 1 mL of Beriplast® P for the surgeon. If Beriplast® P is taken straight from refrigeration, preparation for use takes approximately 10 minutes. Clearly, larger volumes do take longer to prepare.

How should I prepare Beriplast® P?

- Keep the vials the right way up in the cardboard rack or stand during reconstitution (fluid vial up).
- Ventilate the vial – break the vacuum – by inserting the needle pointing towards the bottom corner of the vial, before attaching the syringe.
- Do not invert the vial – use slow, even suction to draw materials out of the vial.

What are the important steps for rapid availability of Beriplast® P?

Preparation in advance is important for rapid availability of Beriplast® P. Ensure that the components are at room temperature and that the syringes are ready for use when needed. To avoid clogging, it is helpful not to assemble the whole delivery device (the spray tip for the Pantajet® or the cannula) too soon.

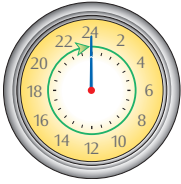
How long before use can I prepare Beriplast® P?

- Reconstituted Beriplast® P, still contained within the sterile blister pack, must be used within 24 hours.
- Once reconstituted and removed from the sterile blister pack, Beriplast® P should be used within 8 hours.

Storage and preparation

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When is the product no longer stable for use?



If stored at between 15 and 25°C, reconstituted Beriplast® P is stable for up to 24 hours in the sterile pouches and for up to 8 hours outside the sterile pouches. After this time, it should be disposed of safely.

What happens if the vials are mixed before the components have reached room temperature?

Beriplast® P reconstitutes best if the diluents are near or at room temperature when they are mixed with the active components. If dissolving is incomplete, the process can be accelerated by rolling the vial in the palms of one's hands or by gently swirling the vial – but again take care not to shake it.

How should I dispose of unused Beriplast® P?

The disposal of unused Beriplast® P will vary according to individual hospital's policy.

What sort of side effects are possible and what advice should post-operative nursing staff be given?

Since 1992, there have been very few cases of reported adverse events attributable to Beriplast® P – fewer than 1 in 250,000 uses was associated with an allergic reaction.

However, it is important to remember that because the aprotinin component of Beriplast® P is derived from a bovine source, hypersensitivity or allergic reaction may occur in rare cases. Symptoms include dyspnoea, flushing, rash, urticaria, hypotension and, in some cases, shock. Should an allergic reaction or anaphylaxis occur, standard anti-allergic therapies should be initiated.

Use of excessive amounts of Beriplast® P may result in unwanted tissue adhesion; therefore only the minimum amount needed should be used and all other areas should be covered during the application of the sealant.

Safety and tolerability

What precautions have been taken to ensure that the product is safe?

Many key steps have been put in place to ensure the safety of Beriplast® P. These include:

- safety at source – careful selection of donors meeting and exceeding all regulatory requirements
- careful testing of donated blood – all donations undergo serology testing as well as PCR (polymerase chain reaction) tests that allow the detection of extremely small amounts of viral particles
- computerised tracking at all stages of manufacture
- comprehensive steps to ensure that the product is free from contaminants – processes include pasteurisation (heating at 60°C for 10 hours) and several other purification steps
- batch testing of final product.

As a result of these safety processes, Beriplast® P is safer than blood transfusion.¹⁵

Stringent **donor and donation testing**, **pasteurisation** and **purification** and final testing are undertaken to ensure that **Beriplast® P** is **safer** than blood-bank products.

How many cases of sealant-related infection have there been observed since launch?

Since launch, many millions of patients have received Beriplast® (P or HS as in Germany), and there have been no proven cases of transmission of viral hepatitis or HIV transmission linked to its use.¹⁶

For a review of the clinical uses of Beriplast® P please refer to:

- Dunn CJ, Goa KL. Fibrin sealant. A review of its use in surgery and endoscopy. *Drugs* 1999;58:863–886.

References

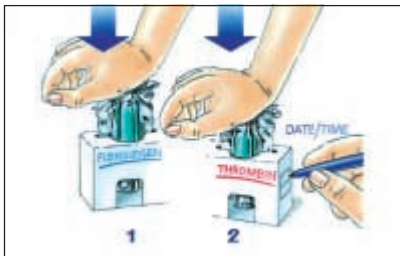
1. Probst M. Fibrin adhesives in modern surgery. *Biomedical Progress* 1989;1:13–16.
2. Kim HJ, Choi YH, Kim HM. The clinical use of fibrin glue. Report of 20 cases. *Korea University Medical Journal* 1988;25(2): 549–553.
3. Mouritzen C, Drömer M, Keinecke H-O. The effect of fibrin glueing to seal bronchial and alveolar leakages after pulmonary resections and decortications. *European Journal of Cardiothoracic Surgery* 1993;7:75–80.
4. Athanasiadis S, Kuhlgtatz C, Girona I. Additional fibrin glueing in surgery of colon and rectum [in German]. *Zentralblatt für Chirurgie* 1984;109(17):1107–1111.
5. Muto T, Ishibiki K, Hatakeyama K, et al. Efficacy and safety of BI 91.021.3 in patients receiving anastomotic surgery [in Japanese]. *Shinyaku to Rinsho* 1994;43:2274–2283.
6. Gnjidic Z, Tomac D, Negovetic L, et al. Fibrin sealants in the management of cerebrospinal fistulae. *Biomedical Progress* 1994;7:39–42.
7. Takakura K, Kubo T, Tajika Y, et al. Efficacy and safety of the use of BI 91.021.3 (Beriplast) in cranial nerve surgery [in Japanese]. *Shinryo to Shinyaku* 1994;31(10):1808–1817.
8. Van Velthoven V, Clarici G, Auer LM. Fibrin tissue adhesive sealant for the prevention of CSF leakage following trans-sphenoidal microsurgery. *Acta Neurochirurgica Wien* 1991;109:26–29.
9. Lee K-C, Park S-K, Lee K-S. Neurosurgical application of fibrin adhesive. *Yonsei Medical Journal* 1991;32(1):53–57.
10. Kohno H, Nagasue N, Chang Y-C, et al. Comparison of topical hemostatic agents in elective hepatic resection: a clinical prospective randomized trial. *World Journal of Surgery* 1992;16:966–970.
11. Dimo B, Jørgensen T, Kjaergaard J, et al. Randomized trial of fibrin adhesive for reduction of drained secretion after elective cholecystectomy. *Acta Chirurgica Scandinavia* 1989;155:177–178.
12. Ohwada S, Ogawa T, Tanahashi Y, et al. Fibrin glue sandwich prevents pancreatic fistula following distal pancreatectomy. *World Journal of Surgery* 1998;22(5): 494–498.
13. Friedrichs O. Submucosal fibrin adhesion – early elective therapy for treatment of peptic ulcer bleeding [in German]. *Endoskopie Heute* 1994;7(1):16–22.
14. Data on file, Aventis Behring GmbH, PO Box 1230, D-35002 Marburg, Germany.
15. Schreiber GB, Busch MP, Kleinmann SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. *New England Journal of Medicine* 1996;334:1685–1690.
16. Joch C, Witzke G et al. Clinical safety of fibrin sealants. Poster presentation at the IXth World Congress of Cardio-Thoracic Surgeons, Lisbon, Portugal, 14–17 November 1999.

Handling

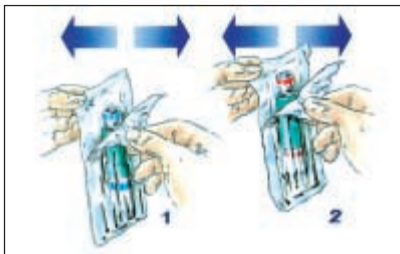
Circulator



- 1 Remove Combi-Set from storage (+2 °C to +8 °C) and bring to room temperature.



- 2 Press down on both parts of Combi-Sets together. Leave the Combi-Set in the sterile package. Write the date and time on the side of the package. Let stand for a few minutes.

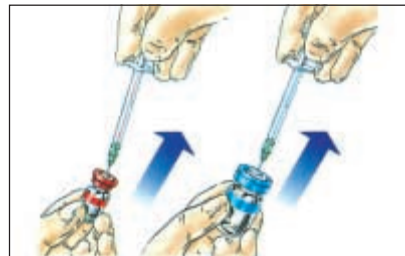


- 3 Remove the plastic wrapping.

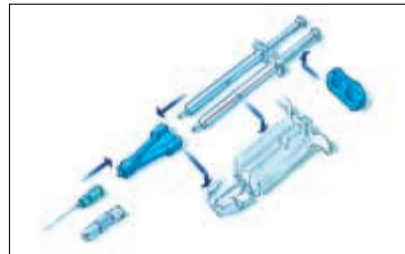
Scrub



- 4 Remove the plastic transfer piece (green plastic part) together with the top bottle.



- 5 Draw up the fibrinogen solution (blue vial) into the application syringe (blue scale). Draw up the thrombin solution (red vial) into the application syringe (red scale).



- 6 Ready for use.

Basic Information

Beriplast® P Combi-Set

is a two-component adhesive containing human fibrinogen concentrate and human thrombin concentrate. The two components are first reconstituted and then sequentially applied to the target surface area. Simultaneous application can be achieved by using the Pantaject® ("dual-syringe") system, in combination with application cannulas, spray-tips, catheters for endoscopic use or other methods.

For covering large wound surfaces Beriplast® P can be sprayed using the enclosed spray-tips, or used in combination with collagen fleece. The tissues requiring adhesion should be fixed in place for several minutes until provisional adhesion is achieved.

Beriplast® P Combi-Set

1/3 ml

Fibrin Adhesive Set
– prescription only –

Composition:

Beriplast® P 1 ml contains:

Combi-Set I consisting of

Vial 1: fibrinogen concentrate (lyophilized) containing 90 mg fibrinogen (human plasma fraction), and 60 U coagulation factor XIII (human plasma fraction), human albumin, L-arginine hydrochloride, L-iso-leucine, sodium chloride, sodium citrate dihydrate, sodium L-glutamate monohydrate connected via transfer device to

Vial 2: aprotinin solution 1 ml, containing 1000 KIU of bovine lung aprotinin corresponding to 0.56 PEU, sodium chloride, water for injections.

Combi-Set II consisting of

Vial 3: thrombin (human plasma fraction) with an activity of 500 I.U., sodium chloride, sodium citrate dihydrate connected via a transfer device to

Vial 4: calcium chloride solution for Beriplast® P 1 ml; solution containing 5.9 mg calcium chloride, water for injections.

Beriplast® P 3 ml contains three times the amount of the above mentioned quantities, respectively.

Indications:

Beriplast® P can be used locally as supportive treatment in all surgical disciplines, including endoscopic specialties to achieve tissue adhesion/sealing, suture support and haemostasis. It can further be used for haemostasis in endoscopic treatment of bleeding gastroduodenal ulcers.

Contraindications:

Arterial and heavy venous bleeding.
Known hypersensitivity to bovine proteins or other constituents of the product.

Special warnings and special precautions for use:

Beriplast® P may only be used for local administration. Beriplast® P 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.

Care is to be taken that parts of the body outside of 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 of the product. On local injection by endoscopic treatment of gastrointestinal bleedings such tissue damage can lead to formation of intramural haematoma. Abdominal pain, nausea, or vomiting within 1 to 3 days after such endoscopic treatment with injection can constitute symptoms of intramural haematoma. In patients with intramural haematoma of the duodenal wall, pancreatitis has been reported in single literature cases. Nevertheless, differential diagnosis for pancreatitis should be carefully evaluated.

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 B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 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. Beriplast® P 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 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.

Undesirable effects:

In rare cases, hypersensitivity or allergic reactions (e.g. dyspnoea, flush/rash, urticaria, hypotension) may occur, extending in isolated cases as far as 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.

Drug interactions:

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

Dosage:

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 of intended application, and the number of applications.

Application of Beriplast® P must be individualised by the treating physician. The initial volume of Beriplast® P to be applied at a chosen anatomic site or target surface should be sufficient to entirely cover the intended application area.

Administration:

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

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

The application can be repeated, if necessary.

Storage and stability:

Beriplast® P is to be stored and protected from light at a refrigerated temperature of +2 to +8 °C. Do not use after expiration date given on the package and containers.

Once reconstituted the thrombin and fibrinogen solutions remain stable in the vials at +15 to +25 °C for 24 hours if stored in the unopened sterile blister packaging or for 8 hours if stored outside the sterile blister packaging.

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.

Additional information:

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 fetus, the course of gestation and peri- and postnatal development.

Only limited experience regarding the administration of Beriplast® P in pregnant women is available.

Presentation:

Beriplast® P Combi-Set is available in packages of 1 ml and 3 ml.