

TISSEEL VH FIBRIN SEALANT TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT

DESCRIPTION

TISSEEL VH, Two-Component Fibrin Sealant, Vapor Heated, Kit (TISSEEL VH Fibrin Sealant), contains the following substances in four separate vials:

1. Sealer Protein Concentrate (Human), Vapor Heated, freeze-dried
2. Fibrinolysis Inhibitor Solution (Bovine)
3. Thrombin (Human), Vapor Heated, freeze-dried
4. Calcium Chloride Solution

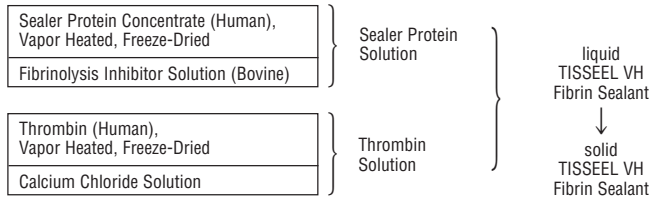
Sealer Protein Concentrate (Human), Vapor Heated is formulated as a sterile, non-pyrogenic, freeze-dried, vapor-heated powder preparation made from pooled human plasma. Fibrinolysis Inhibitor Solution (Bovine) is formulated as a sterile, non-pyrogenic solution containing 3,000 kallikrein inhibitor units (KIU)/mL of Aprotinin, an inhibitor of proteases including plasmin. After reconstitution of the lyophilized Sealer Protein Concentrate in Fibrinolysis Inhibitor Solution, the resulting Sealer Protein Solution contains:

Total protein:	100 – 130 mg/mL
Fibrinogen:	75 – 115 mg/mL
Fibrinolysis Inhibitor:	2250 – 3750 KIU/mL
Excipients:	see table below

Thrombin (Human), Vapor Heated is formulated as a sterile, non-pyrogenic, freeze-dried, vapor-heated powder preparation made from pooled human plasma. Calcium Chloride Solution is formulated as a sterile, non-pyrogenic solution containing 40 µmol/mL CaCl₂. After reconstitution of the lyophilized Thrombin in Calcium Chloride Solution, the resulting Thrombin Solution contains:

Thrombin (Human):	400 – 600 I.U./mL
Calcium Chloride:	36 – 44 µmol/mL
Excipients:	see table below

The Sealer Protein Solution and Thrombin Solution are then combined by using the DUPLOJECT Preparation and Application System, or equivalent delivery device cleared by FDA for use with TISSEEL VH Fibrin Sealant, to form the Fibrin Sealant:



TISSEEL VH Fibrin Sealant is supplied in four different kit sizes of 0.5, 1.0, 2.0 and 5.0 mL, containing the following components:

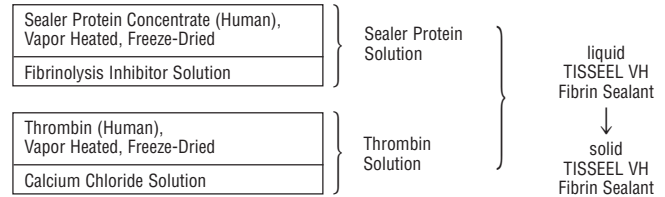
		Package Sizes			
		0.5 mL	1.0 mL	2.0 mL	5.0 mL
Sealer Protein Concentrate	Fibrinogen (mg):	37.5–57.5	75–115	150–230	375–575
	Total Protein (mg):	50–65	100–130	200–260	500–650
	Polysorbate 80 (mg):	0.1–0.2	0.2–0.4	0.4–0.8	1–2
	Sodium Chloride (mg):	1–2	2–4	4–8	10–20
	Trisodium Citrate (mg):	2–4	4–8	8–16	20–40
Fibrinolysis Inhibitor Solution	Aprotinin (KIU):	1125–1875	2250–3750	4500–7500	11250–18750
	Volume (mL):	0.5	1.0	2.0	5.0
Thrombin	Thrombin (IU):	200–300	400–600	800–1200	2000–3000
	Total Protein (mg):	22.5–27.5	45–55	90–110	225–275
	Sodium Chloride (mg):	4–6	8–12	16–24	40–60
	Glycine (mg):	1.2–1.8	2.4–3.6	4.8–7.2	12–18
Calcium Chloride Solution	CaCl ₂ (µmol):	18–22	36–44	72–88	180–220
	Volume (mL):	0.5	1.0	2.0	5.0
Total Combined Volume (mL):		1.0	2.0	4.0	10.0

Source Plasma obtained from US licensed plasma collection centers is used to produce **Sealer Protein Concentrate** and FEIBA* bulk powder, the starting material of **Thrombin**. To obtain **Sealer Protein Concentrate**, the cryoprecipitate derived from Source Plasma is washed, dissolved in buffer solution, filtered and freeze-dried. **Fibrinolysis Inhibitor Solution** is produced from sterile, non-pyrogenic Aprotinin bulk solution obtained from Bayer. **Thrombin** is prepared by dissolving FEIBA bulk powder and incubating the solution with calcium chloride in order to activate prothrombin to thrombin, followed by ultra/diafiltration, sterile filtration and freeze drying. The **Calcium Chloride Solution** is prepared from calcium chloride complying with the specifications listed in the US Pharmacopeia (USP).

The Sealer Protein Concentrate and Thrombin are made from pooled human plasma. The two-step vapor heat treatment used in their manufacture has been shown to be capable of significant viral reduction. No procedure, however, has been shown to be completely effective in removing viral infectivity from derivatives of human plasma (see **Clinical Pharmacology and Warnings**). TISSEEL VH Fibrin Sealant is intended only for topical administration.

* Final product, Anti-Inhibitor Coagulant Complex, FEIBA VH, manufactured by Baxter Healthcare Corporation from the same bulk, is licensed and distributed in the U.S.A. for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and B patients with inhibitors.

Freeze-dried Sealer Protein Concentrate and Thrombin are reconstituted in Fibrinolysis Inhibitor Solution and Calcium Chloride Solution, respectively. The Sealer Protein Solution and Thrombin Solution are then combined by using the DUPLOJECT Preparation and Application System, or equivalent delivery device cleared by FDA for use with TISSEEL VH Fibrin Sealant, to form the Fibrin Sealant:



Use separate syringes for reconstituting Sealer Protein Solution and Thrombin Solution and for applying the two solutions to prevent premature clotting.

Preparation of Sealer Protein Solution

- Freeze-dried Sealer Protein Concentrate is reconstituted in the Fibrinolysis Inhibitor Solution of 3,000 KIU/mL Aprotinin.
- Remove the flip-off caps from the vial containing the Sealer Protein Concentrate and the vial containing the Fibrinolysis Inhibitor Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry. **Do not use iodine containing preparations such as betadine for disinfection.**
- Reconstitute the freeze-dried Sealer Protein Concentrate in the Fibrinolysis Inhibitor Solution by using the FIBRINOTHERM heating and stirring device, a standard incubator, or a water-bath.

Reconstitution of Freeze-Dried Sealer Protein Concentrate Using the FIBRINOTHERM:

(Preferred mode of reconstitution)

For ease of handling, the FIBRINOTHERM, a combined heating and stirring device, has been developed (the vial of freeze-dried Sealer Protein Concentrate contains a magnetic stirrer). Heating and stirring can be operated independently. The FIBRINOTHERM device maintains a constant temperature of 37°C and has been designed to hold the various vial sizes of freeze-dried Sealer Protein Concentrate and Fibrinolysis Inhibitor Solution.

- Insure that the stirrer is initially switched off (green switch).
- Place the vials containing the freeze-dried Sealer Protein Concentrate and the Fibrinolysis Inhibitor Solution into the appropriate openings of the FIBRINOTHERM device and turn the heater on (amber switch). Wait until the signal lamp goes out indicating that the Fibrinotherm device has reached 37°C. Preheat the vials for 10 minutes after this point.
- Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein Concentrate using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with TISSEEL VH Fibrin Sealant (see directions provided with the device system for specific reconstitution instructions). Gently swirl the vial to ensure that the freeze-dried material is completely soaked.
- Place the vial into the largest opening of the FIBRINOTHERM device using the appropriate adaptor. Turn on the stirrer (green switch) and stir the contents for 8 – 10 minutes.
- Reconstitution of the freeze-dried Sealer Protein Concentrate is complete as soon as no undissolved particles are visible. Otherwise, return the vial to the FIBRINOTHERM device and agitate for a few more minutes until the solution appears homogeneous.

Note:

- Do not use the Sealer Protein Concentrate until it has fully dissolved. If the Sealer Protein Concentrate has not dissolved within 20 minutes using the FIBRINOTHERM device, discard the vial and prepare a fresh kit.
- If not used promptly, keep the Sealer Protein Solution at 37°C without stirring. To ensure homogeneity, switch on the stirrer of the FIBRINOTHERM device shortly before drawing up the solution.

Reconstitution of Freeze-Dried Sealer Protein Concentrate Using a Water-Bath:

- Preheat the vials containing the freeze-dried Sealer Protein Concentrate and the Fibrinolysis Inhibitor Solution to about 37°C (but not beyond 40°C).
- Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein Concentrate using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with TISSEEL VH Fibrin Sealant (see directions provided with the device system for specific reconstitution instructions).
- Allow the vial to stand at 37°C for one minute.
- Swirl briefly and vigorously with a circular motion (avoid excessive frothing) and place the vial into a water-bath for another 10 – 15 minutes.
- Reconstitution of the freeze-dried Sealer Protein Concentrate is complete as soon as no undissolved particles are visible. Otherwise, swirl again briefly and keep the vial at 37°C for a few more minutes.
- Draw up the reconstituted Sealer Protein Solution into a sterile syringe using aseptic technique.

Note:

- If a water-bath is used for reconstitution instead of the FIBRINOTHERM device, special precautions have to be taken against submersing the vial, particularly the septum, to avoid possible contamination.
- Do not use the Sealer Protein Concentrate until it has fully dissolved.
- If not used promptly, keep the Sealer Protein Solution at 37°C. To ensure homogeneity, swirl with a circular motion (avoiding frothing) before drawing up the solution.

Reconstitution of Freeze-Dried Sealer Protein Concentrate Using an Incubator:

- Preheat the vials containing the freeze-dried Sealer Protein Concentrate and the Fibrinolysis Inhibitor Solution in an incubator to a temperature of 37°C (but not beyond 40°C) and keep them at this temperature for 10 minutes.
- Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein Concentrate using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with TISSEEL VH Fibrin Sealant (see directions provided with the device system for specific reconstitution instructions).
- Return the vial with the Sealer Protein Concentrate to the incubator and keep it at 37°C for one minute.

CLINICAL PHARMACOLOGY

The TISSEEL VH Fibrin Sealant kit contains Fibrinogen (Sealer Protein Concentrate) and Thrombin as the main active ingredients. It also contains Calcium Chloride Solution, and Fibrinolysis Inhibitor Solution (Aprotinin, bovine). The two reconstituted components, the Sealer Protein Solution and Thrombin Solution, are mixed and applied topically as described in **Dosage and Administration**. Mixing the Sealer Protein Solution and Thrombin Solution produces a viscous solution that quickly sets into an elastic coagulum.

Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein Concentrate into fibrin. Most of the thrombin is adsorbed by the fibrin so formed. Excess thrombin, if any, is inactivated by protease inhibitors in the blood.

Fibrinolysis Inhibitor Solution (Aprotinin) is a polyvalent protease inhibitor which prevents premature degradation of fibrin. Released aprotinin and its metabolites are eliminated by the kidney. (Its half-life in blood is known to average between 30 to 60 minutes.¹ Preclinical studies with different Fibrin Sealant preparations simulating the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of Aprotinin in the product formulation increases resistance of the Fibrin Sealant clot to degradation in a fibrinolytic environment.^{2, 3, 4, 5}

To examine the risk of bovine sensitization, Fibrinolysis Inhibitor Solution was injected intravenously into sensitized guinea pigs.⁶ None showed shock symptoms. No case of clinically manifest bovine sensitization was observed in any of the clinical studies. Rare cases of possible or probable sensitization have been reported with respect to TISSEEL VH Fibrin Sealant or a similar product marketed within the United States or internationally. The physician should be aware of the possibility of sensitization to bovine-derived protein.

The manufacturing procedure for TISSEEL VH Fibrin Sealant includes processing steps designed to reduce the risk of viral transmission. In particular, a two-step vapor heating process is included in the manufacturing of Sealer Protein Concentrate and Thrombin. Validation studies were conducted using samples drawn from manufacturing intermediates for each of the two human plasma derived components, Sealer Protein Concentrate and Thrombin. These samples were spiked with stock virus suspensions of known titers followed by further processing under conditions analogous to those in the respective manufacturing steps.

The virus reduction factors (expressed as log₁₀) of independent manufacturing steps were as follows for each of the viruses tested:^{7, 8}

Reduction Factors for Virus Removal and/or Inactivation during the Manufacture of Sealer Protein Concentrate (Human)

Manufacturing Step	Virus Reduction Factor of Virus Tested				
	HIV-1	TBEV	PRV	ERV-1	HAV
Cryoprecipitation and Washing of Precipitate	2.6	1.3	1.5	1.8	n. d.
Freeze-Drying	1.2	1.3	2.1	3.2	3.0
Vapor Heating	>4.7	>5.6	>4.8	>4.0	>3.0

n. d. = not determined

Reduction Factors for Virus Removal and/or Inactivation during the Manufacture of Thrombin (Human)

Manufacturing Step	Virus Reduction Factor of Virus Tested				
	HIV-1	TBEV	PRV	ERV-1	HAV
Cryoprecipitation	1.4	1.0	1.1	1.0	n. d.
Adsorption on DEAE-Sephadex	2.0	3.0	3.1	1.0	n. d.
Freeze-Drying	2.0	1.0	2.6	1.9	2.7
Vapor Heating	>4.6	>7.0	>4.8	>4.7	>3.9

n. d. = not determined

TISSEEL Fibrin Sealant was evaluated in an open-label crossover study against control topical hemostatic agents in 489 patients undergoing cardiovascular reoperation or resectionotomy at 11 institutions.^{9, 10, 11} Patients were randomized to TISSEEL Fibrin Sealant or control hemostatic agents when a topical hemostatic was needed at the conclusion of surgery and after all attempts at surgical hemostasis. Patients were crossed to the alternative therapy if bleeding continued after the 5 minute endpoint. At 10 centers, TISSEEL Fibrin Sealant was used after administration of protamine sulfate. At one site, TISSEEL Fibrin Sealant could be used before administration of protamine sulfate. For the primary endpoint, successful hemostasis at 5 minutes, TISSEEL Fibrin Sealant was statistically significantly superior to control topical hemostatic agents:

Hemostasis within 5 minutes	
TISSEEL Fibrin Sealant	Control Topical Hemostatic Agent
159/246 (65%)	76/243 (31%)
Pearson χ^2 , two sided; p <0.0001; intent-to-treat analysis	

Similarly, absolute time to cessation of bleeding was statistically significantly shorter for TISSEEL Fibrin Sealant than for control topical hemostatic agents (p<0.0001, Wilcoxon-Gehan test, two sided, Monte Carlo option).

In a single center, prospective open label study of 120 patients randomized to standard of care (59 patients) or standard of care plus Fibrin Sealant (61 patients) for elective colostomy closure after temporary colostomy placement for treatment of traumatic injury to the colon, TISSEEL Fibrin Sealant plus standard of care was shown to be statistically significantly superior to standard of care alone (p = 0.0406, Jonckheere-Terpstra test for ordinal data, two sided) with regard to anastomotic complications (leakage, intra-abdominal abscess formation, re-operation, septic shock, and death).¹²

In a single center, open label trial, TISSEEL Fibrin Sealant was compared to historical controls in patients undergoing laparotomy for blunt or penetrating traumatic injury to the spleen and/or liver.¹³ Use of TISSEEL Fibrin Sealant resulted in the need for statistically significantly fewer splenectomies than control hemostatic maneuvers:

Splenectomy Rate			
Injury to:	TISSEEL Fibrin Sealant	Historic Controls	
Spleen	0/19	14/22	p <0.001
Spleen and liver	1/26	19/34	p <0.001

TISSEEL Fibrin Sealant did not result in statistically significantly reduced mortality in patients with blunt or penetrating trauma to the liver alone or to the liver and spleen (p = 0.067, χ^2 , one sided).

INDICATIONS AND USAGE

TISSEEL VH Fibrin Sealant is indicated for use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating

- Swirl briefly but avoid excessive frothing. Then return the vial into the incubator for another 10 – 15 minutes.
- Reconstitution is complete as soon as no undissolved particles are visible. Otherwise swirl the vial again and return it to the incubator for another 3 – 5 minutes.

Note:

- Do not use the Sealer Protein Concentrate until it has fully dissolved.
- If not used promptly, keep the Sealer Protein Solution at 37°C. To ensure homogeneity, swirl with a circular motion (avoid frothing) before drawing up the solution.

Preparation of Thrombin Solution

Freeze-dried Thrombin is reconstituted in the Calcium Chloride Solution.

- Remove the flip-off caps from the vial containing Thrombin and the vial containing Calcium Chloride Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry. **Do not use iodine containing preparations such as betadine for disinfection.**
- Transfer the contents of the vial with Calcium Chloride Solution into the vial containing the freeze-dried Thrombin using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with TISSEEL VH Fibrin Sealant (see directions provided with the device system for specific reconstitution instructions).
- Swirl briefly. Keep the Thrombin Solution at 37°C until used. Draw up an amount of Thrombin Solution equal to the amount of Sealer Protein Solution that will be used into a sterile syringe using aseptic technique.

Note:

- Do not use the transfer devices, e.g., syringes, previously used for reconstitution of the freeze-dried Sealer Protein Concentrate to prevent premature setting.
- The entire preparation procedure may take up to 40 minutes; therefore, TISSEEL VH Fibrin Sealant must be prepared well in advance of its intended use. Do not use the TISSEEL VH Fibrin Sealant components more than 4 hours after reconstitution.

Transferring to the Sterile Field

For transfer of the Sealer Protein Solution and the Thrombin Solution to the sterile field, the scrub nurse should withdraw the solutions while the circulating nurse holds the unsterile vials.

Note:

- The solutions should be withdrawn slowly by firm constant aspiration to reduce the risk of large air bubbles.

Method of Application

Apply TISSEEL VH Fibrin Sealant by using the DUPLOJECT Fibrin Sealant Preparation and Application System or an equivalent delivery device cleared by FDA for use with TISSEEL VH Fibrin Sealant. Specific instructions for the use of TISSEEL VH Fibrin Sealant in conjunction with each cleared delivery device are provided with the device.

In order to avoid excess formation of granulation tissue and slow absorption of TISSEEL VH Fibrin Sealant, only apply thin layers of the two components.

To prevent TISSEEL VH Fibrin Sealant from adhering to gloves and instruments, wet these with saline before contact with the product.

Application of TISSEEL VH Fibrin Sealant must be completed within 4 hours after reconstitution. Discard any unused product.

- After the two components have been applied, fix or hold the sealed parts in the desired position for at least three to five minutes to ensure that the setting TISSEEL VH Fibrin Sealant adheres firmly to the surrounding tissue.

HOW SUPPLIED

TISSEEL VH Fibrin Sealant is supplied in 4 kit sizes:

- TISSEEL VH, Fibrin Sealant, Two-Component Fibrin Sealant, Vapor Heated, Kit, 0.5 mL
- TISSEEL VH, Fibrin Sealant, Two-Component Fibrin Sealant, Vapor Heated, Kit, 1.0 mL
- TISSEEL VH, Fibrin Sealant, Two-Component Fibrin Sealant, Vapor Heated, Kit, 2.0 mL
- TISSEEL VH, Fibrin Sealant, Two-Component Fibrin Sealant, Vapor Heated, Kit, 5.0 mL

Each kit contains:

- 1 vial of Sealer Protein Concentrate (Human), Vapor Heated, freeze-dried, sterile
- 1 vial of Fibrinolysis Inhibitor Solution (Bovine), sterile, 3000 KIU of Aprotinin/mL
- 1 vial of Thrombin (Human), Vapor Heated, freeze-dried, sterile, 500 I.U./mL
- 1 vial of Calcium Chloride Solution, sterile, 40 μ mol/mL
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Devices for preparation and application of TISSEEL VH Fibrin Sealant are available from Baxter Healthcare Corporation.

Rx only

STORAGE

Store at refrigerator temperature (2°C to 8°C, 35°F to 46°F). Avoid freezing.

Do not use after the expiration date.

ACCESSORIES

FIBRINOTHERM, a combined warming and stirring device for reconstitution of freeze-dried Sealer Protein Concentrate can be obtained from Baxter Healthcare Corporation.

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trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical.^{9, 13, 14, 15, 16} TISSEEL VH Fibrin Sealant is not indicated for the treatment of massive and brisk arterial bleeding.

TISSEEL VH Fibrin Sealant has been shown to be an effective sealant as an adjunct in the closure of colostomies.¹²

TISSEEL VH Fibrin Sealant is a satisfactory hemostatic agent in fully heparinized patients undergoing cardiopulmonary bypass.⁹

CONTRAINDICATIONS

TISSEEL VH Fibrin Sealant is contraindicated in individuals who are known to be hypersensitive to bovine protein.

To avoid a risk of allergic-anaphylactoid reaction and/or thromboembolic events, which may be life-threatening, do not inject TISSEEL VH Fibrin Sealant into a vessel or tissue.

WARNINGS

TISSEEL VH Fibrin Sealant is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses (see **Clinical Pharmacology**). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to the U.S. distributor, Baxter Healthcare Corporation, telephone # 1-800-423-2862. The physician should discuss the risks and benefits of this product with the patient.

TISSEEL VH Fibrin Sealant contains Fibrinolysis Inhibitor Solution (Aprotinin) of bovine source. U.S.D.A. restrictions preclude the use of this product in domestic livestock, such as poultry, cattle, sheep, swine, horses, etc.

PRECAUTIONS

General

Since the Sealer Protein Solution and Thrombin Solution can be denatured by contact with solutions containing alcohol, iodine, or heavy metal ions, they should not be applied before the wound surface is cleaned to remove any antiseptics that may contain such substances.

Because of their low pH, oxycellulose-containing preparations may reduce the efficacy of TISSEEL VH Fibrin Sealant and should not be used as carrier materials. The safety and efficacy of the combined use of TISSEEL VH Fibrin Sealant with other biocompatible carrier materials has not been evaluated in controlled clinical trials.

If a water-bath is used for reconstitution instead of the FIBRINOTHERM, a combined heating and stirring device, special precautions have to be taken against submersing the vial, particularly the septum, to avoid possible contamination.

Information for Patients

Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women or immune-compromised individuals. Symptoms of parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash, and joint pain. Patients should be encouraged to consult their physician if such symptoms appear.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of TISSEEL VH Fibrin Sealant or studies to determine the effect of TISSEEL VH Fibrin Sealant on fertility have not been performed.

Pregnancy Category C

Animal reproduction studies have not been conducted with TISSEEL VH Fibrin Sealant. It is also not known whether TISSEEL VH Fibrin Sealant can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TISSEEL VH Fibrin Sealant should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

As with any other plasma derivatives, anaphylactoid or anaphylactic reactions may occur in rare cases. No adverse events of this type were reported during the course of the clinical trials.

Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

In cases of hypersensitivity to bovine proteins (Aprotinin), or after repeated administration of TISSEEL VH Fibrin Sealant or systemic administration of Aprotinin, allergic or anaphylactic reactions can occur on rare occasions, if no pre-medication is given. Even if the second treatment with TISSEEL VH Fibrin Sealant was well tolerated, a subsequent administration of TISSEEL VH Fibrin Sealant or systemic administration of Aprotinin may result in severe anaphylactic reactions. Symptoms associated with allergic/anaphylactic reactions include flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock.

In the event of hypersensitivity reactions, administration of TISSEEL VH Fibrin Sealant is to be discontinued and state-of-the-art emergency measures are to be taken (following the guidelines of modern therapy).

In rare cases, these reactions may also occur in patients receiving Aprotinin or TISSEEL VH Fibrin Sealant for the very first time.

INTERACTIONS

None known.

DOSAGE, ADMINISTRATION, PREPARATION, AND APPLICATION OF THE COMPONENTS

TISSEEL VH Fibrin Sealant is to be administered only topically. The required dose of TISSEEL VH Fibrin Sealant depends on the size of the surface to be covered, as in the following table:

Maximum size of the area to be sealed	Required package sizes of TISSEEL VH Fibrin Sealant
4 cm ²	0.5 mL
8 cm ²	1.0 mL
16 cm ²	2.0 mL
40 cm ²	5.0 mL

The TISSEEL VH Fibrin Sealant kit contains the following substances in four separate vials:

1. Sealer Protein Concentrate (Human), Vapor Heated, freeze-dried
2. Fibrinolysis Inhibitor Solution (Bovine)
3. Thrombin (Human), Vapor Heated, freeze-dried
4. Calcium Chloride Solution

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Issued 04/2003
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U.S. Pat. No. 4,640,834
U.S. Pat. No. 4,395,396
U.S. Pat. No. 4,359,049
U.S. Pat. No. 5,714,370
Other U.S. patents pending

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