PRODUCT MONOGRAPH

TISSEEL KIT VH

Two-Component Fibrin Sealant (Human), Vapor Heated

Freeze-Dried Powders with Diluents for Local Application

Two-Component Fibrin Sealant

Hemostatic Agent

Manufactured by:
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Imported and Distributed by:
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ACTION AND CLINICAL PHARMACOLOGY

TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, is a tissue glue with sealing, hemostyptic and gluing properties, which does not interfere with but may enhance wound healing.

Numerous clinical studies investigating the safety and efficacy of the product as a hemostyptic and biodegradable tissue glue in various fields of surgery have been performed. A number of these were controlled studies in fields including orthopedic surgery[1], abdominal surgery[2], urology[3], and cardiovascular surgery[4, 5]. The recently concluded cardiovascular safety study[10] using the heat treated product has shown that TISSEEL transmits neither hepatitis viruses nor HIV. Pre-clinical studies have shown that the vapor treated product is at least as effective as the heat treated product.

Use of the Sealant has invariably shown superior results in the groups treated as against the untreated controls who underwent the same types of surgery. These results were attributable to an improved hemostasis and, therefore, reduced blood loss, a tighter sealing of sutures preventing leakages or a fast and uncomplicated healing of the surgical wound.

In none of the studies have systemic side-effects been seen nor has any product related transmission of viral hepatitis or HIV occurred in any of the patients treated.

INDICATIONS AND CLINICAL USE

TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, is used, in addition to standard measures, to achieve hemostasis, to seal or glue tissue, and to support wound healing.

Indications include:
abdominal surgery[2, 6, 7]
cardiovascular surgery[4, 5, 8, 9]
orthopedic surgery[1, 10]
thoracic surgery[11, 12, 13]
urology[3, 14, 15, 16]

CONTRAINDICATIONS

TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, alone is not indicated for the treatment of severe or brisk arterial or venous bleeding.

Known hypersensitivity to bovine protein or to any constituents of the product, including aprotinin.

WARNINGS

This product is manufactured using components of human blood which may contain the causative agent of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized in blood collection centres and the plasma testing laboratories are designed to reduce the risk of transmitting viral infection. However, the risk of viral infectivity from this product cannot be totally excluded.

TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, should not be applied intravascularly, since this can lead to intravascular coagulation and may result in life-threatening thromboembolic complications and might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients. Especially in coronary bypass surgery, TISSEEL KIT VH should be applied with caution to minimize any risk of intravascular application.
However, if in well-founded cases the injection of Tisseel and/or Thrombin Solution/s into a tissue or vessel is indicated, careful risk/benefit analysis of the individual case is to be carried out.

In the submucous injection of fibrin sealant into hollow organs (stomach, duodenum), the following points are to be considered:

1. Insertion of the needle into the organ wall may result in accidental perforation, which in rare cases may injure adjoining organs or vessels.

2. No case of thromboembolic events following accidental vessel puncture and intravascular injection of fibrin sealant has so far been observed in the treatment of ventricular or duodenal ulcers, but cannot be excluded with certainty.

3. Injection into the submucous membrane may cause a mechanical dissection between the tunica mucosa and the tunica muscularis propria, which in rare cases may lead to vessel injury or the formation of an intramural hematoma.

Injection into highly vascularized tissue, such as nasal mucosa, must be avoided, as severe allergic-anaphylactoid reactions have been seen and thromboembolic events may occur. Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.
If fibrin sealants are applied in confined spaces, the risk of compressive complications should be taken into account.

As with any protein product, allergic-type hypersensitivity reactions are possible with TISSEEL KIT VH. Manifestations of hypersensitivity reactions to TISSEEL observed include: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnea, nausea, urticaria, angioedema, pruritus, erythema, paresthesia. Fatal anaphylactic reactions including anaphylactic shock, have also been reported with TISSEEL. At the first sign or symptom of a hypersensitivity reaction, TISSEEL application must be stopped and medical care initiated. Remaining product must be removed from the sites of application.

TISSEEL KIT VH contains bovine aprotinin, a polypeptide known to be associated with anaphylactic reactions. Even in the case of strict local application of aprotinin, there is a risk of anaphylactic reactions to aprotinin, particularly in the case of previous exposures. As with other aprotinin-containing products, the use of TISSEEL should be documented in the patient's records, pointing out that TISSEEL contains aprotinin.

Because this product is made from human plasma, a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob prion) cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The risk of transmitting 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/or removing viruses.

The measures taken are considered effective for inactivation/removal of enveloped viruses such as HIV, HBV, and HCV, and for the nonenveloped virus HAV. These measures may be of limited value against small nonenveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (fetal infection); however there are no adequate data from the use of TISSEEL in pregnant and lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing TISSEEL.

Parvovirus B19 infection may also be serious for individuals with immunodeficiency or increased red blood cell turnover.

Safety and effectiveness of the product in pediatric patients has not been established.

PRECAUTIONS

Neither of the two components, separately or combined, should be administered by the intravascular route, or thromboembolic complications will occur.

This product must not be used in animals.

The user is cautioned against the spray application of TISSEEL KIT VH, Sealer Protein Concentrate (Human), Vapor Heated, with devices produced by other manufacturers. The TISSEEL control device and the Spray Set may be obtained from Baxter.

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

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

Application Precautions

Apply TISSEEL as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

When applying TISSEEL using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 20-25 psi. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying TISSEEL changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

The sealer protein and thrombin solutions can be denatured by alcohol, iodine or heavy metal ions (e.g. antiseptic solutions). If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of TISSEEL.

Neurosurgical Procedures
The safety and effectiveness of TISSEEL used alone or in combination with biocompatible carriers in neurosurgical procedures or other surgeries involving confined spaces have not been evaluated.

Drug Interactions
Are not known. The Sealant can even be applied in fully heparinised patients (e.g. extracorporeal circulation).

See *WARNINGS AND PRECAUTIONS* and *DOSAGE AND ADMINISTRATION* sections for substances that can denature the sealer protein and thrombin solutions.

Oxycellulose-containing preparations may reduce the efficacy of TISSEEL KIT VH and should not be used as carrier materials.
TISSEEL KIT VH must not be mixed with other medicinal products.

ADVERSE REACTIONS

TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, should not be applied intravascularly, since this can lead to intravascular coagulation and may result in life-threatening thromboembolic complications and might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients. Especially in coronary bypass surgery, TISSEEL KIT VH should be applied with caution to minimize any risk of intravascular application.
However, if in well-founded cases the injection of Tisseel and/or Thrombin Solution/s into a tissue or vessel is indicated, careful risk/benefit analysis of the individual case is to be carried out.

In very rare cases allergic and/or anaphylactic reactions may occur in patients with a history of hypersensitivity against bovine protein and/or in the event of repeated administration. If symptoms require treatment to be initiated, this should be effected in the usual manner, as for instance with antihistamines, corticoids or adrenalin.

Post-marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC).

IMMUNE SYSTEM DISORDERS: hypersensitivity reactions, including anaphylactic reactions, anaphylactic shock, and the following manifestations: angioedema, paresthesia, bradycardia, tachycardia, flushing, bronchospasm, dyspnea, wheezing, urticaria, pruritus, and erythema. Anaphylactic reactions and anaphylactic shock have included fatal outcomes.

VASCULAR DISORDERS: Thromboembolism, including cerebral artery embolism and venous thrombotic cerebral infarction as a result of intravascular application.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Impaired wound healing.

Other adverse reactions associated with fibrin sealant/hemostatic products include, as manifestations of hypersensitivity or allergic reactions, application site irritation, chest discomfort, chills, headache, lethargy, restlessness, and vomiting.

There have been rare reports of air embolism associated with misapplication of fibrin sealant using a spray device.

DOSAGE AND ADMINISTRATION

TISSEEL KIT VH is for topical (i.e., epilesional) use only, do not inject. TISSEEL KIT VH must not be applied intravascularly (see *WARNINGS AND PRECAUTIONS*).

The required dose of Tisseel Thrombin Solution depends on the purpose of use and on the size of the surface to be sealed or coated or on the size of the defect to be packed. When used for adherence, only a thin layer of TISSEEL should be applied to avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant. Excessive thickness of the fibrin layer may negatively interfere with the product's efficacy and the wound healing process. If used for tissue adherence, it is recommended that the initial application cover the entire intended application area. As a rule, TISSEEL KIT VH 1.0, Two-Component Fibrin Sealant (Human), Vapor Heated, will provide for sealing of approximately 10 cm^2 when using the Application Needle, and 25 cm^2 – 100 cm^2 when using the Spray Set.

It is desirable for Tisseel to be absorbed slowly during the wound healing process. For that reason, Aprotinin Solution is used for reconstitution of the freeze-dried Tisseel Sealer Protein Concentrate. The concentration of the Aprotinin Solution supplied with the Kit may be varied to control the rate at which TISSEEL will be absorbed. If the Aprotinin Solution is diluted with Sterile Water for Injection, TISSEEL will be absorbed faster. This may also be desirable if a recipient surface is known to have a low fibrinolytic activity of its own.

The setting rate of the Tisseel Thrombin Solution, on the other hand, depends on the concentration of the Thrombin Solution used. While the Tisseel Thrombin Solution may take up to one minute to set with a thrombin concentration of 4 IU/ml, this setting process will be complete within seconds if the higher Thrombin concentration of 500 IU/ml is used. The higher thrombin concentration may be advantageous to achieve hemostasis, while the lower thrombin concentration is better apt to seal tissue because it allows time for approximation of the wound areas.

The application can be repeated, if necessary. However, avoid reapplication of TISSEEL KIT VH to a pre-existing polymerized TISSEEL KIT VH layer as TISSEEL KIT VH will not adhere to a polymerized layer. Separate, sequential application of the two components of Tisseel must be avoided.

It is recommended that every time a patient receives a dose of TISSEEL KIT VH the name and batch number of the product are documented in order to maintain a record of the batches used.

Various methods can be used to apply the two components of TISSEEL:

Simultaneous application
a) using Duploject and Application Needle
b) using Duploject and Spray Head
c) using Duploject and Application Catheters
d) by premixing

Note: Simultaneous application by premixing requires a low thrombin concentration of 4 IU/ml. Either concentration is suitable for applications using Duploject.

1. How to Prepare Tisseel Solution

Freeze-dried Tisseel Sealer Protein Concentrate is reconstituted in the Aprotinin Solution of 3,000 KIU/ml. To obtain lower concentrations, dilute the Aprotinin Solution with Sterile Water for Injection.

E.g., to obtain a concentration of 100 KIU/ml dilute 0.1 ml (0.2 ml if TISSEEL KIT VH 5.0 is used) with 3 ml (5 ml) of Sterile Water for Injection using the blue-scaled syringe.

Prior to application, TISSEEL must be warmed to 33-37ºC. TISSEEL must not be exposed to temperatures above 37ºC and must not be microwaved.

Reconstitution of Freeze-Dried Tisseel Sealer Protein Concentrate Using Fibrinotherm:
For ease of handling, a combined heating and stirring device, Fibrinotherm, has been developed to meet the specific requirements of reconstituting freeze-dried Tisseel Sealer Protein Concentrate. Fibrinotherm is a thermoblock with a magnetic stirrer (the vials for freeze-dried Tisseel Sealer Protein Concentrate contain a magnetic spin propeller to stir the contents). Heating and stirring can be operated independently. In a first step, Fibrinotherm heats up to 37°C and then maintains that temperature constantly with minimum variation. Fibrinotherm has been designed to hold the various vial sizes of freeze-dried Tisseel Sealer Protein Concentrate and Aprotinin Solution.

- Place vials containing freeze-dried Tisseel Sealer Protein Concentrate and Aprotinin Solution into the appropriate openings of the Fibrinotherm and operate flip switch. Wait until signal lamp goes out. Fibrinotherm has now reached 37°C. Preheat vials for ten minutes.
- Transfer Aprotinin Solution into vial containing freeze-dried Tisseel Sealer Protein Concentrate using blue-scaled syringe of corresponding size (or syringe that has been used for dilution of Aprotinin Solution).

Note: Only combine **preheated** Aprotinin Solution with **preheated** Tisseel Sealer Protein Concentrate.

- Place vial into largest opening of Fibrinotherm (if necessary, use adaptors). Turn on stirrer with flip switch and stir contents for 8 – 10 minutes.
- Reconstitution of freeze-dried Tisseel Sealer Protein Concentrate is complete as soon as no undissolved particles are detectable in transparent light. Otherwise, replace into Fibrinotherm and agitate for another few minutes until the solution appears homogeneous.

Note: If not used immediately, keep Tisseel Solution at 37°C without stirring. To ensure homogeneity switch on stirrer of Fibrinotherm shortly before drawing up the solution.

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

- Preheat the vial with freeze-dried Tisseel Sealer Protein Concentrate and the vial with the Aprotinin Solution to about 37°C (but not beyond 40°C).
- Transfer Aprotinin Solution into vial containing freeze-dried Tisseel Sealer Protein Concentrate using blue-scaled syringe of corresponding size (or syringe that has been used for dilution of Aprotinin Solution).
- Allow vial to stand at 37°C for one minute.
- Swirl briefly and vigorously with a circular motion (avoid excessive frothing) and replace vial into water-bath for another 10 – 15 minutes.
- Reconstitution of freeze-dried Tisseel Sealer Protein Concentrate is complete as soon as no undissolved particles are detectable in transparent light. Otherwise, swirl again briefly and keep vial at 37°C for a few more minutes.

Draw up reconstituted Tisseel Solution into a sterile blue-scaled syringe using aseptic precautions (insert a needle through the rubber stopper at its center to allow access of air).
Note: If not used immediately, keep Tisseel Solution at 37°C. To ensure homogeneity, swirl with a circular motion (avoid frothing) before drawing up the solution.

2. How to Prepare Thrombin Solution

Depending on the desired thrombin concentration, either transfer the contents of the vial with Calcium Chloride Solution into the vial containing freeze-dried Thrombin 500 (quick solidification) or Thrombin 4 (slow solidification).

Use one of the sterile black-scaled syringes for preparing Thrombin Solution.

Swirl briefly. Keep Thrombin Solution at 37°C until used. Draw up an amount of Thrombin Solution equal to the amount of Tisseel Solution into a sterile black-scaled syringe using aseptic precautions.
Note: Do not use the syringes and needles previously used for reconstitution of freeze-dried Tisseel Sealer Protein Concentrate to prevent premature setting.

3. Application[17]

Before application, the surface of the wound should be as dry as possible.

The sealer protein and thrombin solutions can be denatured by alcohol, iodine, or heavy metal ions. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of TISSEEL KIT VH.

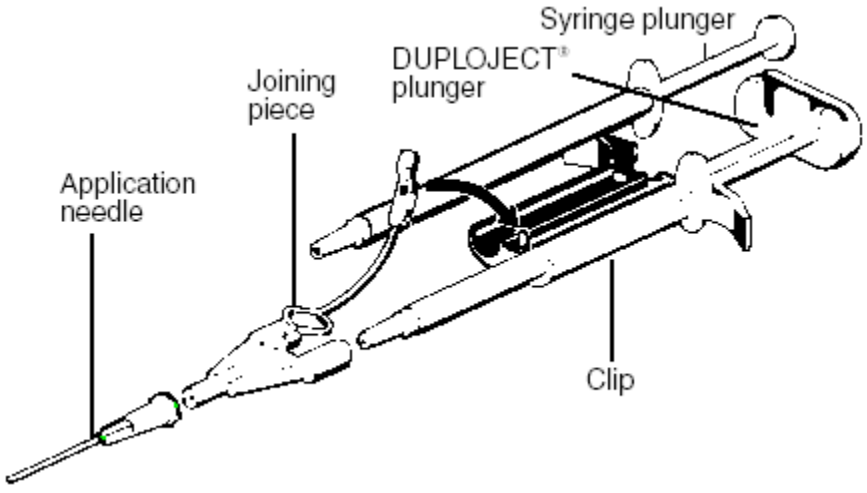
Oxycellulose-containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials.

Application beyond the intended area of application should be avoided.

Simultaneous Application Using DUPLOJECT-System:
The Duploject allows simultaneous application of the two components and ensures that they are quickly and thoroughly mixed, which is essential for TISSEEL to gain the optimum strength. Either Thrombin concentration can be used.

a) Simultaneous Application Using Duploject and Application Needle:

The sterile Duploject consists of a clip for two identical disposable syringes and a common plunger which ensures that equal volumes of the two components are fed over a common joining piece before being mixed in the Application Needle and ejected.

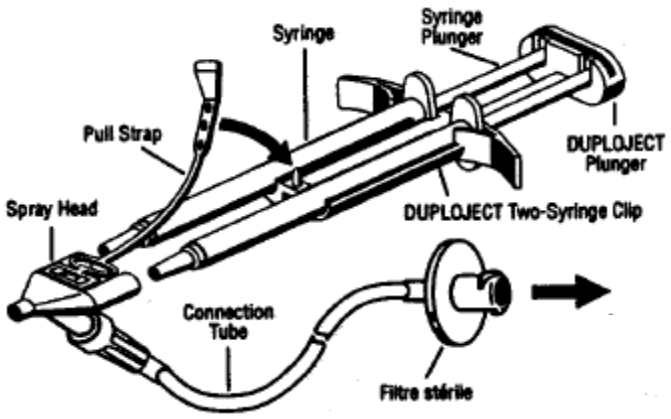


Operating instructions:

- Place syringes filled with Tisseel and Thrombin Solutions into the clip. Both syringes should be filled with equal amounts and should not contain any air bubbles.
- Connect the nozzles of the two syringes with the Joining Piece. Ensure firm hold. Secure the Joining Piece by fastening the strap to the clip.
- Fit Application Needle onto the Joining Piece. Do not remove remaining air from inside the Joining Piece or Application Needle. Otherwise the apertures of the needle may clog before application of the Tisseel Thrombin Solution.
- Apply the Tisseel Thrombin Solution onto the recipient surface or surfaces if two parts of tissue need to be glued together.

Note: Only the syringes contained in the Kit for reconstitution and application are designed to perfectly fit into the Duploject clip. Any other syringe may cause problems since exact and firm adaptation to the Joining Piece cannot be granted for. If the procedure of applying the two components with Duploject is interrupted, replace the Application Needle by a new one when sealing is resumed (three spare needles come with the Kit). Only replace Application Needle immediately prior to resuming sealing. Otherwise, the apertures of the Joining Piece will clog, which requires it to be also replaced (one spare Joining Piece comes with the Kit).
In cases where very small volumes (1 to 2 drops) of TISSEEL KIT VH are administered, expel and discard the first several drops from the application cannula immediately before application, to ensure adequate mixing of the sealer protein and thrombin solutions.

b) Simultaneous Application Using Duploject, Spray Set and TISSEEL:



The spray set is particularly suitable for spraying of larger areas, e.g. to control oozing of parenchymatous organs. Duploject is used for this method of application except that a Spray Head is used instead of the Joining Piece. The two components are sprayed simultaneously using sterile propellent gas via TISSEEL, and the volume of the Solutions ejected is controlled with the Duploject plunger. Spray at a distance of at least 10 – 20 cm. The user is cautioned against the spray application of TISSEEL with devices produced by other manufacturers.

Note: A detailed description of this application method is included in the leaflet of the Spray Set.

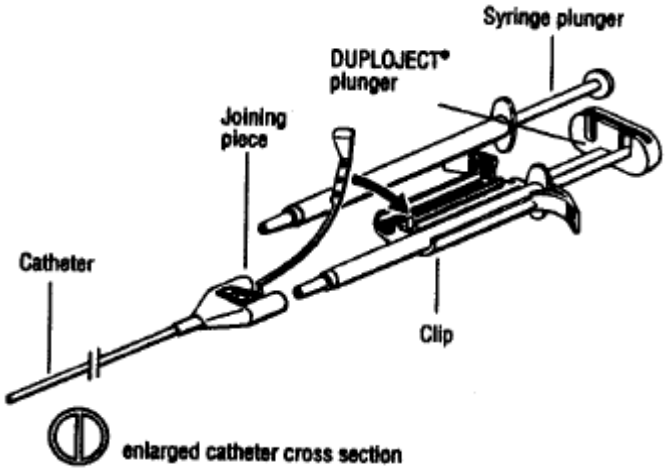
Caution must be used when applying fibrin sealant using pressurized gas because the application of pressurized gas is associated with a potential risk of air embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening.

TISSEEL KIT VH must be sprayed only onto application sites that are visible and must not be used in enclosed body areas.

The user must follow the instructions and precautions in the device user manual, for example regarding the need to limit the gas pressure to a maximum of 2 bars, and is cautioned against the spray application of TISSEEL KIT VH with devices produced by other manufacturers.

c) Simultaneous Application Using Duploject and Application Catheter:

In operation sites where access is difficult or when using an endoscope or trocar, TISSEEL can be applied using Duploject with Application Catheter.



Note: A detailed description of this application method is included in the leaflet of the respective Application Catheter.

d) Simultaneous Application by Premixing:

Mix equal volumes of the two components and immediately apply them to the recipient surface or surfaces. When the low thrombin concentration of 4 IU/ml is used, approximately one minute is allowed for mixing the components, applying them, and approximating the wound areas. If desired, the Tisseel Thrombin Solution can be mixed with spongiosa to pack bone defects. Hold in place for three minutes. Once turbid, TISSEEL can no longer be manipulated.

4. Gluing of Tissue

After the two components have been applied, approximate the wound areas. Fix or hold the glued parts in the desired position for three to five minutes to ensure that the setting Sealant adheres firmly to the surrounding tissue. Solidified Sealant reaches its ultimate strength after about two hours (70% after about ten minutes).

PHARMACEUTICAL INFORMATION

Composition
TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, contains the following substances in five separate vials:

1. Tisseel Sealer Protein Concentrate (Human)[*], sterile, freeze-dried, vapor-heated, reconstituted contains:

Total protein	100-130 mg/ml
Factor XIII	10-50 U/ml[**]
Fibrinogen	70-110 mg/ml
Plasmafibronectin (CIG)	2-9 mg/ml
Plasminogen	40 – 120 µg/ml
2. Aprotinin Solution, sterile, bovine	3,000 KIU/ml[***]
3. Thrombin 4, sterile, freeze-dried, vapor heated, human reconstituted contains	4 IU/ml[****]
4. Thrombin 500, sterile, freeze-dried, vapor heated, human reconstituted contains	500 IU/ml[****]
5. Calcium Chloride Solution, sterile	40 µmol/ml

The Kit also contains an application set consisting of a Duploject-applicator, disposable syringes, two Joining Pieces and four Application Needles. In addition to the Kit, a Spray Set and Application Catheters are available.

Tisseel Sealer Protein Concentrate and Thrombin are made from human plasma. During manufacture they are subjected to a product-specific vapor heat treatment. Preclinical data show that this treatment produces a decrease in HIV-1 titer of 10^6 or more infectious units per ml.

Individual donations of human plasma are combined to form plasma pools. Prior to being used for manufacture of TISSEEL, each plasma pool is tested for the presence of genome sequences of the human immunodeficiency virus type 1 (HIV-1), hepatitis B virus (HBV) and hepatitis C virus (HCV) using the HIQ-PCR.[*****]

The action of TISSEEL simulates key features of the physiological process of wound closure. A highly concentrated fibrinogen aprotinin solution, which among other ingredients contains Factor XIII, and a solution of thrombin and calcium chloride are applied to the wound area, where the mixture coagulates. The presence of Factor XIII causes the fibrin to crosslink, which gives the coagulum additional resilience.

The substances in the Kit are used to prepare two components: Tisseel Solution and Thrombin Solution. Tisseel Solution is produced by dissolving Tisseel Sealer Protein Concentrate in Aprotinin Solution. Freeze-dried Thrombin, dissolved in Calcium Chloride Solution, yields the Thrombin Solution.

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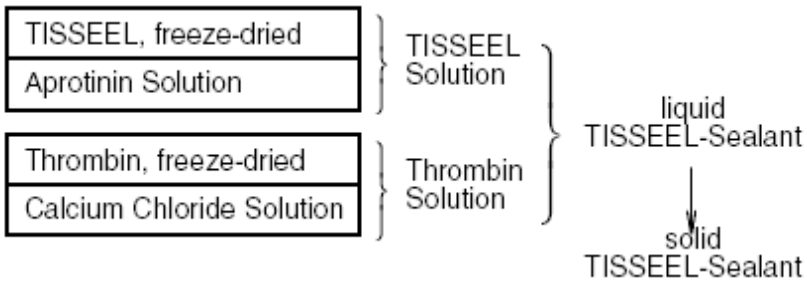
[*] Each vial contains a magnetic spin propeller to facilitate reconstitution when placed in the FIBRINOTHERM warming and stirring device.

[**] One unit corresponds to the amount of Factor XIII contained in 1 ml of fresh normal plasma.

[***] 30 Kallidinogenase Inactivator Units (KIU) correspond to 1 FIP-Unit[18].

[****] One International Unit (IU) of Thrombin is defined as the activity contained in 0.0853 mg of the First International Standard of Human Thrombin[19].

[*****] HIQ-PCR = Hyland Immuno Quality Assured Polymerase Chain Reaction
With this method 500 genome equivalents/ml of the above viruses can be determined reliably, with the actual sensitivity of HIQ-PCR being below that. Therefore all pools which have been tested and evaluated as being positive lead to exclusion from further processing. No correlation has been demonstrated between infectivity and removal of pools containing these levels of genomic equivalents from further manufacturing.



The two components are mixed either immediately before application to the recipient surface or *in situ* using one of the methods described under **Application.** Tisseel Thrombin Solution is a viscous solution adhering to wound surfaces and quickly sets to form a white, rubberlike mass, which continues to gain in strength within two hours following application. This process is made use of to achieve hemostasis, and to seal or glue tissue.

In this manner, the need for sutures may be reduced, although not totally eliminated. The time until Sealant sets can be used to approximate wound edges, to provide optimum conditions for healing. In the course of wound healing, Sealant is completely absorbed[20].

To prevent the transmission of infective agents by the administration of TISSEEL, prescribed procedures are used for the collection and testing of the source plasma and during the manufacture of the product. They include measures taken for donor and plasma selection[*], as well as virus removal and inactivation steps during manufacturing.

The efficiency of these manufacturing steps employed during the production of TISSEEL has been demonstrated in validation studies using human immunodeficiency virus (HIV), hepatitis A virus, and model viruses for hepatitis B and hepatitis C viruses (HBV, HCV) as well as for non-enveloped viruses[21, 22, 23].

In an international multicenter safety study, coagulation factor concentrates that were virus-inactivated by steam treatment showed no evidence of transmission of hepatitis viruses or HIV[24, 25].

Pharmaco-epidemiological surveillance of TISSEEL has shown no product-related transmission of infective agents[26].

Stability and Storage Recommendations
When stored between 2°C and 8°C (35°F and 46°F), TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, is stable until the expiry date indicated on the label.

Reconstituted Solutions
Reconstituted Tisseel and Thrombin Solutions must be used within four hours. Reconstituted solutions must not be refrigerated or frozen.

AVAILABILITY OF DOSAGE FORMS

TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated, is supplied in the following three pack sizes:

TISSEEL KIT VH, 1.0 for 1.0 ml of reconstituted Tisseel Solution and 1.0 ml Thrombin Solution

[*] All plasma units used for manufacture are ALT tested and non-reactive in tests for Hbs-antigen and antibodies to HCV, HIV-1 and HIV-2. Before further processing all individual plasma donations are subjected to an inventory hold for a possible look-back of plasma donations suspected of infection.

TISSEEL KIT VH, 2.0 for 2.0 ml of reconstituted Tisseel Solution and 2.0 ml Thrombin Solution
TISSEEL KIT VH, 5.0 for 5.0 ml of reconstituted Tisseel Solution and 5.0 ml Thrombin Solution

Accessories
The following accessories can be obtained from a Baxter representative:

FIBRINOTHERM:	Combined heating and stirring device for the reconstitution of freeze-dried Tisseel Sealer Protein Concentrate.

Accessories for the use of DUPLOJECT with Spray Set:

TISSEEL:	Propellent gas control unit including foot switch, manometer, reducing valve, and pressure tube.
SPRAY-SET (sterile, disposable):	Disposable set consisting of sterile filter with connection tube and a spray head.

Accessories for the use of DUPLOJECT with Application Catheter:

DUPLOCATH 25 Application Catheter:	Length: approximately 25 cm (10“) Diameter: approximately 5 french (approx. 0.17 cm) Radiopaque.
DUPLOCATH 35 M.I.S.:	Catheter: Length: approximately 35 cm (14“) Diameter: approximately 5 french (approx. 0.17 cm) Adapter: Length: approximately 30 cm (12“) Diameter: 15 french (0.5 cm) For insertion through a 5-6 mm trocar in minimally invasive surgery (M.I.S.) Radiopaque. Sterile. Disposable.
DUPLOCATH 180 Application Catheter:	Length: approximately 180 cm (70”) Diameter: approximately 5 french (approx. 0.17 cm) For use with an endoscope. Radiopaque. The Application Catheter 180 can be shortened to any length necessary.

PHARMACOLOGY

The therapeutic activities of TISSEEL KIT VH, Two Component Fibrin Sealant (Human), Vapor Heated, are hemostasis, gluing and sealing of tissue, and the support of wound healing.

Physiologically, the process of wound closure sets in when a bleeding ceases. In places where injured blood vessels lie open, hemostatic plugs form of platelets and fibrin, which become more and more solid as other blood cells, particularly erythrocytes, are involved. Because the bleeding ceases, blood that has escaped into the wound bed earlier coagulates. In a next step fibrin in both the coagulated blood and hemostatic plug retracts, plasma is squeezed out, the blood vessels contract, and the wound area becomes smaller. As various cells begin to proliferate into the retracted blood coagula, wound healing sets in.

In developing Fibrin Sealant, this principle has at least partly been simulated by applying a highly concentrated fibrinogen solution, which contains factor XIII, and a solution of thrombin and calcium chloride to the wound area, where the mix coagulates. Since the Sealant does not contain thrombocytes, the clotted fibrin does not appreciably retract. When the mixture is applied, however, the fibrin concentration in the coagulum is the same as or higher than that of a retracted hemostatic plug. To hold the coagulum until the wound healing has reached a stage where it is no longer required, the Sealant has been designed to contain a fibrinolysis inhibitor.

The fibrin in the Sealant adheres perfectly to the wound edges guaranteeing adequate sealing effect. Similar to the hemostatic plug, wound healing is promoted by the fibrin applied. Combined application of Sealant with a mixture of autologous or homologous spongiosa provides excellent plugging material for bone defects. Using the adequate technique, TISSEEL is also an excellent tool in sealing autologous or homologous cartilage and bone.

TISSEEL and all of its components have not been observed to affect systemic circulation, respiration, or the central nervous system. This is attributable to both, the fact that only minimal quantities of each single component are applied compared to their use for other indications, and the fact that TISSEEL becomes only locally effective.

The mechanism underlying solidification of tissue and persistence of a solidified clot have been investigated in numerous studies.

As a biologic material, Fibrin Sealant becomes completely absorbed at a rate which depends both on the fibrinolytic activity of the surrounding tissue and the quantity of Fibrinolysis Inhibitor added. In the course of wound healing the Sealant clot is gradually replaced by ingrowing tissue, Thrombin is inactivated by the physiological protease inhibitors, Calcium Chloride is subjected to the calcium and chloride catabolism of the organism, and Aprotinin and its metabolites are eliminated by the kidney.

TOXICOLOGY

The local application of TISSEEL KIT VH, Two-Component Fibrin Sealant (Human), Vapor Heated underlines the importance of histological studies for toxicology data. Accordingly, histologies have been performed on various species in tissues ranging from skin, vessels, nerves, tendons, organ tissue to bone.

Because TISSEEL is a locally active agent and is usually used in single applications, little value can be attributed to the investigation of acute, subacute and subchronic toxicity. Also, animals are a poor choice for such studies, since the main components, Sealer Protein Concentrate and Thrombin, are preparations of human origin, which may be antigenic in animals.

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