

TISSEEL Fibrin Sealant VH S/D (frozen)

Two-component Fibrin Sealant, Deep-Frozen, Vapour Heated (VH) and Solvent Detergent (S/D) treated, TISSEEL VH S/D¹

DESCRIPTION

The active ingredients of TISSEEL are formulated as two sterile, deep-frozen solutions, the Sealer Protein Solution and Thrombin Solution (see Table 1 and PRESENTATION). Each solution is presented in a separate preloaded chamber of one double-chamber syringe. The active ingredients are fractionated from pooled human plasma.

TABLE 1: Composition of the Active Ingredients of TISSEEL

1. Sealer Protein Solution: 1mL of the solution contains

<i>Active ingredients</i>	
As total protein	96 - 125mg
thereof: Fibrinogen/Clottable Protein	72 - 110mg
Factor XIII (human)	1.2 - 10IU
Aprotinin, synthetic (Fibrinolysis Inhibitor)	3000KIU ²
<i>Excipients (see Table 2)</i>	

Aprotinin (synthetic) is manufactured by solid phase synthesis from materials completely of non-human/non-animal origin.

2. Thrombin Solution: 1mL of the solution contains

<i>Active ingredients</i>	
Thrombin (human)	500IU ³
Calcium chloride (2.H ₂ O)	40μmol
<i>Excipients (see Table 2)</i>	

¹ The term 'Vapour Heated (VH) and Solvent Detergent (S/D) treated' is abbreviated as VH S/D.

² KIU = Kallidinogenase Inactivatore Unit.

³ One International Unit (IU) of Thrombin is defined as the activity contained in 0.0853mg of the First International Standard of Human Thrombin.

TABLE 2: Composition of the Excipients of TISSEEL

1. Sealer Protein Solution	1mL of the solution contains, Human Albumin (10 - 20mg), Histidine (10 - 25mg), Sodium Citrate dihydrate (4.8 - 9.7mg), Polysorbate 80 (0.6 - 1.9mg), Nicotinamide (3 - 9mg), Water for injection q.s. to 1mL.
2. Thrombin Solution	1mL of the solution contains, Human Albumin (45 - 55mg), Sodium Chloride (3.5 - 5.5mg) and Water for injection q.s to 1mL.

The two deep frozen solutions comprising TISSEEL must be defrosted prior to use. After thawing and warming up to 37°C, the two solutions are mixed during application (see DOSAGE AND ADMINISTRATION/Method of Application).

Chemical Structures

The major component of the clottable protein (human origin) is fibrinogen. The fibrinogen molecule is a dimer composed of two symmetrical subunits linked by -S-S- bonds. It could be written in a simple formula as $(A\alpha, B\beta, \gamma)_2$ and has a molecular weight (MW) of about 340 000. The $A\alpha$ -chain contains 610 amino acids (MW about 68 000), the $B\beta$ -chain 461 amino acids (MW about 57 000), and the γ -chain 411 amino acids (MW about 47 000). Thus, the entire human fibrinogen contains 2964 amino acids.

Thrombin (human origin) is a glycosylated protein, consisting of two polypeptide subunits A and B, covalently linked by one -S-S- bond. The molecular weight is about 33 800. The human thrombin subunit A chain is made of 36 amino acids, whilst the B chain contains 259 amino acids.

Factor XIII (human origin), also called blood-coagulation factor XIII, is a tetramer composed of two a-chains and two b-chains (each of a molecular weight of about 80 000) which are non-covalently associated.

Aprotinin (synthetic origin) is a protease inhibitor, a polypeptide consisting of one chain of 58 amino acids with a molecular weight of 6511.5, also stabilized by -S-S- bonds.

PHARMACOLOGY

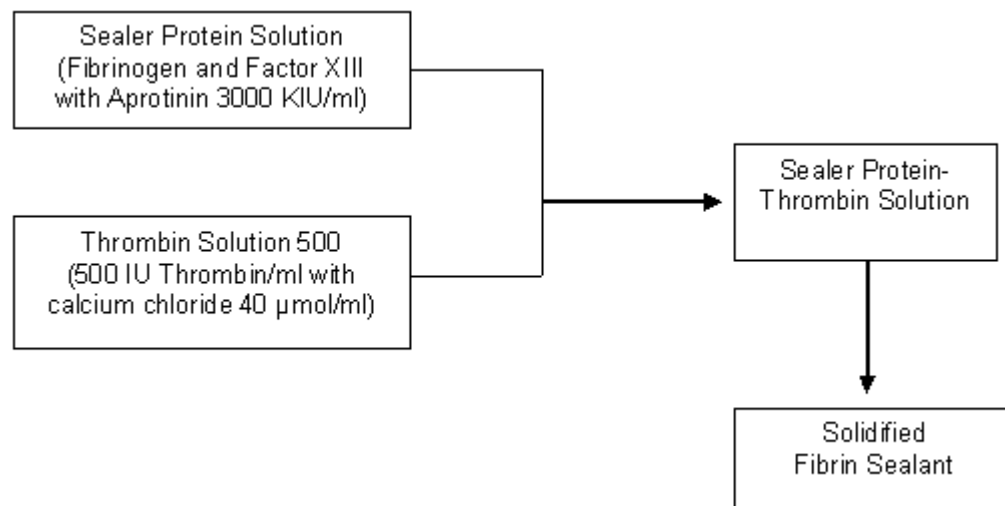
Pharmacodynamics

TISSEEL contains two components, Sealer Protein Solution and Thrombin Solution. The Sealer Protein Solution contains fibrinogen as the main active ingredient; the active ingredient of the Thrombin Solution is human Thrombin.

Thrombin is a highly specific protease that transforms the fibrinogen contained into fibrin monomers. These fibrin monomers are then polymerized in a linear fashion and stabilised by cross-linking (catalysed by factor XIII) to form an insoluble fibrin clot. Aprotinin (synthetic) is a protease inhibitor which prevents the premature degradation of fibrin.

These reactions simulate the key features of the physiological coagulation process. The resulting fibrin clot appears as a white, elastic mass which firmly adheres to tissue and which can be used to achieve haemostasis or seal tissues.

When the two component solutions come into contact, conversion of fibrinogen to fibrin and polymerization and cross-linking of fibrin monomers commences immediately and results in the clotting of the fibrin within seconds. The following diagram illustrates the process.



Pharmacokinetics

Solidified TISSEEL is intended for local application only, therefore systemic exposure or distribution to other organs or tissues is not expected and Pharmacokinetic Studies were not conducted.

Clinical Trials

TISSEEL VH S/D was evaluated in a prospective, parallel design, randomised (1:1), double-blind, multicenter clinical study against an earlier formulation of the product, TISSEEL VH⁴, in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) and median sternotomy. Patients were treated with TISSEEL VH S/D or the control product TISSEEL VH only when haemostasis was not achieved by conventional surgical methods. For the end point, haemostasis achieved at the primary treatment site within 5 minutes of treatment and maintained until closure of the surgical wound, TISSEEL VH S/D was non-inferior to the earlier formulation of the product using a one-sided 97.5% confidence interval on the difference in the proportion of subjects successfully treated.

Haemostasis within 5 minutes and maintained until surgical closure		
	TISSEEL VH S/D	TISSEEL VH
Intent to Treat Analysis	127/144 (88.2%)	129/144 (89.6%)
Per Protocol Analysis	108/123 (87.8%)	122/135 (90.4%)

Virus Safety

To confirm virus safety of TISSEEL VH S/D, subjects were followed up for seroconversion due to virus infections. There were zero confirmed seroconversions for both TISSEEL VH S/D-treated subjects and TISSEEL VH-treated subjects: analysis of B19V seroconversion 1 month after surgery revealed a 0% (0/140) incidence of seroconversion in TISSEEL VH S/D-treated subjects and a 0% (0/138) incidence of seroconversion in TISSEEL VH-treated subjects. Analysis of HAV, HBV, HCV, and HIV-1/-2 six months after surgery revealed a 0% (0/128) incidence of seroconversion in TISSEEL VH S/D-treated subjects and a 0% (0/134) incidence of seroconversion in TISSEEL VH-treated subjects.

An earlier formulation of TISSEEL VH S/D, TISSEEL HT⁵ (Fibrin Sealant heat-treated) was evaluated in an open-label crossover study against control topical haemostatic agents in 489 patients undergoing cardiovascular re-operation or re-sternotomy at 11 institutions. Patients were randomised to TISSEEL HT or control haemostatic agents when a topical haemostatic was needed at the conclusion of surgery and after all attempts of surgical haemostasis. Patients were crossed to the alternative therapy if bleeding continued after the 5 minute endpoint. At 10 centres, TISSEEL was used after administration of protamine sulfate. At one site, TISSEEL could be used before administration of protamine sulfate. 365 of the 489 patients had an eligible bleeding

⁴ Baxter commercialized several single virus inactivated, predecessor fibrin sealant products, utilizing heat treatment (HT) or vapor heat treatment (VH) for virus inactivation. Predecessor products were manufactured both in frozen or lyophilized presentation.

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event, for the primary endpoint, successful haemostasis at 5 minutes, TISSEEL was statistically significantly superior to control topical haemostatic agents:

Haemostasis within 5 minutes	
TISSEEL HT ⁵	Control Topical Haemostatic Agent
159/193 (82.4%)	76/172 (44.2%)
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 than for control topical haemostatic agents ($p < 0.0001$, Wilcoxon-Gehan test, two sided).

In a single centre, prospective open label study of 120 patients randomised 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, the earlier version of TISSEEL⁶ 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).

A review of published literature was conducted studying the repair of defects of the articular cartilage in the knee; ($n = 293$ patients; 166 patients were treated with either Autologous Chondrocyte Implantation (ACI) or Matrix-Induced Autologous Chondrocyte Implantation (MACI); 127 patients were treated with either mosaicplasty or microfracture or abrasive arthroplasty). In all ACI/MACI procedures, TISSEEL Fibrin Sealant was applied topically. The efficacy of TISSEEL has been assessed indirectly by the efficacy outcome measures used to assess joint function following repair of cartilage defects. Outcome measures within the first six months of treatment are considered to be of particular importance because treatment failure attributed to graft movement (e.g., periosteal delamination or detachment of the collagen matrix) typically occurs within the first three to six months following implant. In addition, in the first 6 months post-implant, there were no reports by patients of symptoms which may be indicative of graft instability such as “locking” or “catching” of the knee joint. In one study MRI assessments, made at one and two months, showed that there was a high level of graft integration with the surrounding cartilage, and that grafts were present and in their original position in the majority of patients (15/17). These findings suggest that TISSEEL is an effective adhesive in this indication. Long term results (≥ 6 months) indicated that treatment with either ACI or MACI was at least as successful as the comparative treatment.

⁶ Baxter commercialized several single virus inactivated, predecessor fibrin sealant products, utilizing heat treatment (HT) or vapor heat treatment (VH) for virus inactivation. Predecessor products were manufactured both in frozen or lyophilized presentation.

In a single centre, open label trial, an earlier formulation of TISSEEL⁵ was compared to historical controls in patients undergoing laparotomy for blunt or penetrating traumatic injury to the spleen and/or liver. Use of TISSEEL resulted in the need for statistically significantly fewer splenectomies than control haemostatic manoeuvres:

Splenectomy Rate		
Injury to:	TISSEEL ⁶	Historic Controls
Spleen p < 0.001	0/19	14/22
Spleen and liver p < 0.001	1/26	19/34

TISSEEL 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

TISSEEL is indicated:

- as adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical; and
- as a sealant as an adjunct for closure of colostomies.
- as a sealant and/or adhesive for use in autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) procedures.

CONTRAINDICATIONS

Known hypersensitivity to aprotinin or known hypersensitivity to any other component of TISSEEL.

Injection of TISSEEL into tissues is contraindicated. Such use has been associated with inadvertent intravascular injection, with thromboembolic complications. TISSEEL should be applied with caution to minimise any risk of intravascular application, for example in coronary bypass surgery. TISSEEL should only be applied topically.

PRECAUTIONS

Viral and Prion Risk

Sealer Protein Concentrate and Thrombin are made from human plasma. Products made from human plasma may contain infectious agents which can cause disease, such as viruses and theoretically Creutzfeld-Jacob Disease (CJD) agents. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken (including double virus inactivation by vapour heat treatment and solvent detergent treatment) are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

The measures taken may be of limited value against small non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red blood cell turnover (e.g., haemolytic anaemia).

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

Apply TISSEEL as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process. Air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening, have occurred with the use of spray devices employing a pressure regulator to administer TISSEEL. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

When applying TISSEEL using a spray device, be sure to use the pressure within the pressure range recommend by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 1.4 - 1.7 bars. 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 -15cm from the surface of the tissue. When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism.

General

Administration of TISSEEL may result in allergic reactions in some patients. For patients with a known allergic diathesis, a history of hypersensitivity to medical products or a history of having previously received aprotinin-containing products (including previous use of TISSEEL), a careful risk-benefit assessment should be carried out prior to administration. The risk of immunisation against proteins such as aprotinin is increased if repeat exposure occurs within six months. If it is decided to proceed with treatment in such patients, prior administration of histamines should be considered.

Manifestations of hypersensitivity reactions to TISSEEL observed include: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnoea, nausea, urticaria, angioedema, pruritus, erythema, paresthesia. Fatal anaphylactic reactions, including anaphylactic shock, have also been reported with TISSEEL. Refer ADVERSE EFFECTS. Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

As Sealer Protein and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals (e.g. in disinfectants), any such substances should be removed before application. Refer INCOMPATIBILITIES.

TISSEEL alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.

If possible, cover all tissue adjacent to the site of sealing before applying TISSEEL.

TISSEEL should not be used for the sealing of neuroanastomoses, as the high aprotinin content of the TISSEEL solution delays absorption of the fibrin seal and it cannot be ruled out that this may cause fibrosis.

Injection into the nasal mucosa must be avoided, as severe allergic/anaphylactoid reactions have been observed and thromboembolic complications may occur in the area of the ophthalmic artery.

If fibrin sealants are applied in confined bodily spaces, the risk of compressive complications should be taken into account.

Genotoxicity

Studies of genotoxic potential of TISSEEL have not been performed.

Carcinogenicity

Animal studies to evaluate the carcinogenic potential of TISSEEL have not been performed.

Effects on Fertility

Studies of the effect of TISSEEL on fertility have not been performed.

Use in pregnancy (Category B2)

Animal reproduction studies have not been conducted with TISSEEL. There are no adequate and well-controlled studies in pregnant women. TISSEEL should be used during pregnancy only if clearly needed and potential benefit justifies the potential risk to the foetus.

Use in Lactation

Studies on TISSEEL in lactating animals or women have not been conducted. TISSEEL should be used during lactation only when strictly indicated.

Paediatric Use

Safety and effectiveness of TISSEEL in paediatric patients have not been established. There has been a single report of disseminated intravascular coagulation occurring in a premature infant who received TISSEEL 3mL during a laparotomy for peritoneal adhesions.

Use in the Elderly

Of the total number of subjects in a clinical study of TISSEEL, 71 out of 144 subjects were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Interactions with Other Drugs

There are no known interactions between TISSEEL and other drugs. Efficacy has been demonstrated in fully heparinised patients undergoing cardiopulmonary bypass. Refer INCOMPATIBILITIES for more detailed information on interactions with substances other than drugs.

ADVERSE EFFECTS

Anaphylactic and anaphylactoid reactions may occur in patients who have previously received a fibrin-based sealant, in those with a known hypersensitivity to aprotinin and those who have previously received aprotinin systemically. Even if the second treatment with TISSEEL was well tolerated, a subsequent administration of TISSEEL 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, dyspnoea, severe hypotension, and anaphylactic shock. In the event of hypersensitivity reactions, administration of TISSEEL should be discontinued, the topical clot removed, and appropriate treatment instituted.

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

Injection of TISSEEL into tissues has been associated with inadvertent intravascular administration and thromboembolic complications. Such use is therefore not recommended (see CONTRAINDICATIONS).

The adverse reactions presented in this section were reported from clinical trials investigating the safety and efficacy of TISSEEL. In these trials, TISSEEL was administered for adjunct haemostasis in cardiac, vascular, and total hip replacement surgeries; and for the sealing of lymphatic vessels in patients undergoing axillary lymph node dissection. In these studies, a total of 499 patients were administered TISSEEL. The frequencies are based on the number of cases considered possibly/probably related by investigators.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	Preferred MedDRA Term	Frequency	Number of Cases (Frequency Percentage)
VASCULAR DISORDERS	Hypotension	Uncommon	1 (0.2%)
GASTROINTESTINAL DISORDERS	Nausea	Uncommon	2 (0.4%)
INVESTIGATIONS	Fibrin degradation products increased	Common	7 (1.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Postprocedural pain	Common	7 (1.4%)

Legend: ADR frequency is based upon the following scale: Very Common ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), Very Rare ($< 1/10,000$)

The undesirable effects reported in the listing hereafter are based on post-market experience for this type of product. Their frequency has been evaluated by using the following criteria: very common ($> 1/10$), common ($> 1/100, < 1/10$), uncommon ($> 1/1,000, < 1/100$), rare ($> 1/10,000, < 1/1,000$), and very rare ($< 1/10,000$).

The undesirable effects listed below reflect the type of undesirable effects that have been reported with TISSEEL.

Their incidence rate is $< 1/10,000$, i.e. very rare.

Cardiac disorders

- Bradycardia, tachycardia

Gastrointestinal disorders

- Nausea

General disorders and administration site disorders

- Hypersensitivity reactions

Immune system disorders

- Hypersensitivity reactions (including anaphylactic reactions, anaphylactic shock, and the following manifestations: angioedema, paresthesia, bradycardia, tachycardia, flushing, bronchospasm, dyspnoea, wheezing, urticaria, pruritus, and erythema). Anaphylactic reactions and anaphylactic shock have included fatal outcomes.

Injury, poisoning and procedural complications

- Anaphylactoid reactions

Investigations

- Drop in blood pressure

Respiratory, thoracic and mediastinal disorders

- Dyspnoea

Skin and subcutaneous tissue disorders

- Pruritus, Impaired wound healing

Vascular disorders

- Flush, (severe) hypotension, thromboembolism (including cerebral artery embolism and venous thrombotic cerebral infarction) as a result of intravascular application

Class Effects

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

DOSAGE AND ADMINISTRATION

Dosage

TISSEEL should only be administered topically. **Do not inject.** The required dose of TISSEEL depends upon the size of the surface to be covered. To avoid the formation of excess granulation tissue, and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of TISSEEL should be applied. Excessive thickness of the fibrin layer may negatively interfere with the product's efficacy and the wound healing process.

The application can be repeated, if necessary. However, avoid re-application of TISSEEL to a pre-existing polymerized TISSEEL layer as TISSEEL will not adhere to a polymerised layer. If used for tissue adherence, it is recommended that the initial application cover the entire intended application area.

The approximate surface areas covered by each package size of TISSEEL are listed in the following table.

Maximum size of the area to be sealed	Required package size of TISSEEL
8cm ²	2mL
16cm ²	4mL
40cm ²	10mL

Method of Preparation of TISSEEL Preloaded Syringe (Frozen)

Thaw preloaded syringe in one of the three following options:

Option 1 – Thawing on the sterile field

33°C to 37°C sterile water bath - transfer devices set and the inner pouch to the sterile field, remove devices set with preloaded syringes from inner pouch and place directly into sterile water bath. Ensure the contents of the syringe are completely immersed under the water.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Sterile Water Bath (Pouches Removed)
2mL	5 minutes
4mL	5 minutes
10mL	12 minutes

Option 2 – Thawing off the sterile field

33°C to 37°C non-sterile water bath in two pouches - maintain the devices set in both pouches and place into a water bath off the sterile field for appropriate time. Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch and preloaded syringe onto the sterile field.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Non-Sterile Water Bath (In Pouches)
2mL	30 minutes
4mL	40 minutes
10mL	80 minutes

Option 3 – Thawing off the sterile field

Incubate (33°C to 37°C) in pouches – maintain the devices set in both pouches and place into an incubator for appropriate time. Remove from incubator after thawing and transfer inner pouch and preloaded syringe onto the sterile field.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Incubator (In Pouches)
2mL	40 minutes
4mL	85 minutes
10mL	105 minutes

Do not microwave TISSEEL.

TISSEEL should only be used when, after thawing, the Sealer Protein Solution has a viscous consistency similar to honey (air bubbles in the syringe chamber holding the Sealer Protein Solution slowly rise to the top when the double chamber syringe is tilted or turned upside down). If the Sealer Protein Solution has the consistency of a gel, it must be assumed to have become denatured due to an interruption of the cold storage chain. In this case, the fibrin sealant must not be used.

The protective syringe cap should not be removed until thawing is complete and application tip is ready to be attached. Do not use TISSEEL unless it is completely thawed and warmed (liquid consistency).

The solutions must be used within 72 hours after thawing at 25°C or below.

Any unused product and/or devices should be disposed of in accordance with local requirements.

Method of Application

Application of TISSEEL must be completed within 4 hours after opening the preloaded frozen double chamber syringe. Discard any unused product. Separate, sequential application of the two components of TISSEEL must be avoided.

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

Before application, the surface of the wound should be as dry as possible. If application is interrupted, clogging occurs immediately in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the aperture of the joining piece (Y connector) facing the cannula is clogged, use the spare joining piece provided in the package.

In cases where very small volumes (1 to 2 drops) of TISSEEL 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.

Caution must be used when applying fibrin sealant using pressurized gas.

- Any 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 with the spray set must not be used in enclosed body areas.
- TISSEEL must be sprayed only onto application sites that are visible.
- 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. Do not spray closer than the distance recommended by the spray device manufacturer. The user is cautioned against the spray application of TISSEEL with devices produced by other manufacturers.

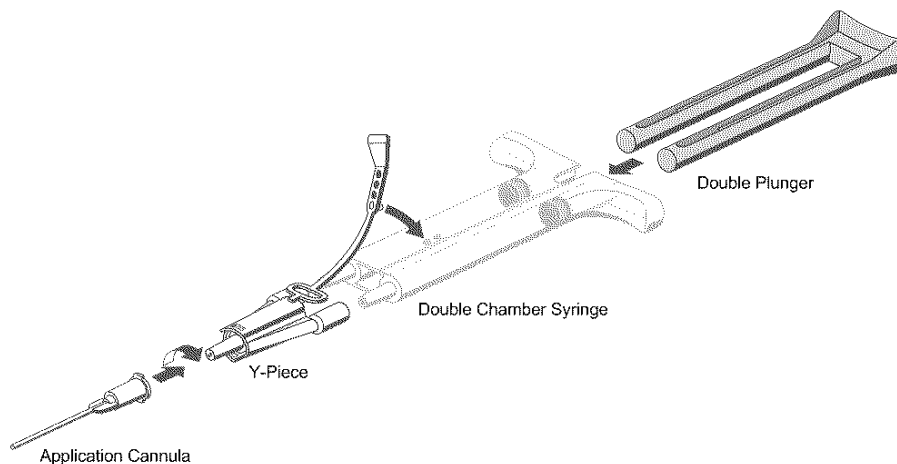
When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism.

Application beyond the intended area of application should be avoided.

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 the setting TISSEEL adheres firmly to the surrounding tissue.

Operating Instructions

For application, connect the double chamber syringe with the Sealer Protein Solution and the Thrombin Solution to a Y-piece and an application cannula (see diagram overleaf) as provided in the accompanying set of devices. The double plunger of the double chamber syringe ensures that the equal volumes are fed through the Y-piece before being mixed in the application cannula and ejected.



Device Set Instructions: firmly connect the double chamber syringe nozzles to the Y-piece and secure it by fastening the tether strap to the syringe. Fit an application cannula onto the Y-piece. To avoid clogging, do not expel the air remaining inside the Y-piece or application cannula until application.

Incompatibilities

Sealer Protein and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of TISSEEL.

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

TISSEEL must not be mixed with other medicinal products.

OVERDOSAGE

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

In the event of overdosage please contact the National Poisons Information Centre (telephone 0800 POISON or 0800 764 766).

PRESENTATION

Nature and Contents of Container

Nature of containers

Both Sealer Protein and Thrombin Solutions are contained in two separate chambers of a single use double chamber syringe made of polypropylene.

Contents

Each pack of TISSEEL contains:

- One single use double chamber syringe, each chamber containing:
 - Chamber number [1]: Sealer Protein Solution (with aprotinin) deep frozen
 - Chamber number [2]: Thrombin Solution (with calcium chloride) deep frozen
- One set of devices (see below).

TISSEEL is available in the following pack sizes:

- TISSEEL, 2.0mL (containing 1.0mL of Sealer Protein Solution and 1.0mL of Thrombin Solution)
- TISSEEL, 4.0mL (containing 2.0mL of Sealer Protein Solution and 2.0mL of Thrombin Solution)
- TISSEEL, 10.0mL (containing 5.0mL of Sealer Protein Solution and 5.0mL of Thrombin Solution)
(see table below for formulation details)

TABLE 3: TISSEEL is supplied in three different package sizes of 2.0, 4.0 and 10.0mL, containing the following components

	Package Sizes	2mL	4mL	10mL
Sealer Protein Solution	Active Ingredients	1mL	2mL	5mL
	As total Protein (mg) thereof:	96 - 125	192 - 250	480 - 625
	Fibrinogen/Clottable protein (mg)	72 - 110	144 - 220	360 - 550
	Factor XIII, human (Unit)	1.2 - 10IU	< 20IU	< 50IU
	Aprotinin, synthetic (KIU)	3000	6000	15000
	Excipients			
	Human albumin (mg)	10 - 20	20 - 40	50 - 100
	Histidine (mg)	10 - 25	20 - 50	50 - 125
	Sodium Citrate (mg)	4.8 - 9.7	9.6 - 19.4	24 - 48.5
	Polysorbate 80 (mg)*	0.6 - 0.9	1.2 - 3.8	3.0 - 9.5
	Niacinamide (mg)	3.0 - 9.0	6.0 - 18.0	15.0 - 45.0
	Volume: water for injections to (mL)	1.0	2.0	5.0
Thrombin Solution	Active Ingredients	1mL	2mL	5mL
	Thrombin, human (IU)	500	1000	2500
	Calcium Chloride (µmol)	40	80	200
	Excipients			
	Sodium Chloride (mg)	3.5 - 5.5	7.0 - 11.0	17.5 - 27.5
	Protein (mg) by addition of Human Albumin ≥ 35 mg/mL)	45 - 55	90 - 110	225 - 275
	Volume: Water for Injections to (mL)	1.0	2.0	5.0
	Combined Volume	2.0	4.0	10.0

* tested on the Drug Substance level

Shelf life

Deep frozen TISSEEL has a shelf life of two years at temperatures < -20°C. The expiry date is stated on the final container and the package.

Unopened pouches, thawed at 25°C or below, may be stored for up to 72 hours at 25°C or below after removal from the freezer. After thawing, the solution must not be refrozen.

If the product is removed from original pouch or warmed to 33 - 37°C, it must be used within 12 hours.

The TISSEEL solutions contain no antimicrobial agent. TISSEEL is intended for single use in one patient only and unused solution in the syringes should be discarded.

Special Precautions for Storage

Store in a freezer (**at -18°C or colder**). The cold storage chain must not be interrupted until use.

Keep container in the outer carton to protect from light.

Keep out of reach and sight of children.

For single use only. Do not re-sterilise!

Set of Devices

Each pack TISSEEL contains a double-sterile set of devices (DUO SET) consisting of one syringe double-plunger, two Y-pieces and four application cannulas. These devices are used for the simultaneous application of the fibrin sealant components. For details on application and complications associated therewith see DOSAGE AND ADMINISTRATION section, heading Operating Instructions using double-chamber syringe, double-plunger, Y-Piece and application cannulas.

The set of devices is sterile and non-pyrogenic in unopened and undamaged package. Sterilised by exposure to ethylene oxide.

MEDICINE CLASSIFICATION

Prescription Medicine.

NAME AND ADDRESS

TISSEEL, Two component Fibrin Sealant, Deep Frozen, Vapour Heated (VH) and Solvent Detergent (S/D) treated, is manufactured by Baxter AG, Vienna, Austria.

Distribution

Baxter Healthcare Ltd
PO Box 14 062
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DATE OF PREPARATION

22 June 2011.

Based on the Australian PI approved 20 October 2010 revised XX Month YYYY.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

TISSEEL, and Duo Set are trademarks of BAXTER AG. BAXTER is a trademark of Baxter International Inc.

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3. LOWE J., *et al.*: Evaluation of the topical hemostatic efficacy and safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: a phase 3, randomized, double-blind clinical study. *J. Cardiovasc Surg.* 2007; 48: 323-331.