

AUSTRALIAN PRODUCT INFORMATION – TISSEEL (APROTININ, FACTOR XIII, FIBRINOGEN, THROMBIN, CALCIUM CHLORIDE DIHYDRATE)

1 NAME OF THE MEDICINE

Aprotinin (synthetic), factor XIII, fibrinogen, thrombin and calcium chloride dihydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients of TISSEEL VH S/D are formulated as two sterile, deep-frozen solutions, the Sealer Protein Solution and Thrombin Solution (see Table 1 below for composition of TISSEEL). 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 TISSEEL

	Sealer protein solution	Thrombin solution
Active Ingredients	-Aprotinin (synthetic) -Factor XIII -Fibrinogen	-Thrombin (human) -Calcium chloride dihydrate
Excipients	-Albumin (human) -Histidine -Nicotinamide -Polysorbate 80 -Sodium citrate -Water for Injections	-Albumin (human) -Sodium chloride -Water for Injections

Table 2: List of active ingredients and associated quantities

	Sealer protein solution	Quantity	Thrombin solution	Quantity
Active Ingredient	Aprotinin (synth)	2250 - 3750 KIU/mL	Thrombin (human) Calcium chloride dihydrate	400 - 625 IU/mL 36 - 44 micromole/mL
	Factor XIII	1.2 - 10 IU/mL		
	Fibrinogen	72 - 110 mg/mL		

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 **DOSE AND METHOD OF ADMINISTRATION** section, heading *Method of Application*).

3 PHARMACEUTICAL FORM

Two-Component Fibrin Sealant, Deep-Frozen, Vapour Heated (VH) and Solvent Detergent (S/D) treated, TISSEEL VH S/D¹. The 2 components of TISSEEL are colourless to pale yellow, opalescent when frozen and clear to slightly turbid solutions once defrosted.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TISSEEL is indicated:

- as adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical
- 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
- for mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

TISSEEL should only be administered topically. **Do not inject. TISSEEL must not be applied intravascularly.** The required dose 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 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 using cannula	Maximum size of the area to be sealed using compressed gas	Required package size of TISSEEL
8 cm ²	100 cm ²	2 mL
16 cm ²	200 cm ²	4 mL
40 cm ²	500 cm ²	10 mL

When TISSEEL is used for mesh fixation it may be applied as drops and/or by a spray technique depending on the preference of the surgeon. Usually the drops of TISSEEL are applied where surgeons routinely position staples and the layer of fibrin sealant achieved with spraying allows the entire mesh to be fixed in place without shrinking and folding.

The quantity of TISSEEL required for mesh fixation depends on the mesh size selected and the recommended amount is the same for different application techniques. For example, 2 – 4mL of reconstituted TISSEEL applied as a thin layer is suitable to adequately fix a standard size mesh of approximately 10 x 15 cm.

When using the drop technique, surgeons should apply TISSEEL at key anchor points for fixing the mesh (e.g. pubic tubercle in inguinal hernia repair) and at the margins of the mesh. Application by spray, either alone or in combination with drops, should cover the mesh uniformly with a thin layer.

In inguinal hernia repair the mesh covering vascular structures and nerves can be fixed with TISSEEL alone using drops and/or spray.

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)	
	DUO AST	PRIMA
2 mL	5 minutes	5 minutes
4 mL	5 minutes	5 minutes
10 mL	12 minutes	10 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)	
	DUO AST	PRIMA
2 mL	30 minutes	15 minutes
4 mL	40 minutes	20 minutes
10 mL	80 minutes	35 minutes

Option 3 – Thawing off the sterile field

Incubator (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)	
	DUO AST	PRIMA
2 mL	40 minutes	40 minutes
4 mL	85 minutes	50 minutes
10 mL	105 minutes	90 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.

Dry the site of application. Before application, the surface area of the wound needs to be dried using standard techniques. Do not use pressurised air or gas for drying the site.

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.

To prevent TISSEEL from adhering to gloves and instruments, wet these with sodium chloride solution before contact.

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 use of adequately mixed product.

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

- any application of pressurized air or 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 Easy Spray device user manual, for example regarding the need to limit the gas pressure to a maximum of 2 bars and not be sprayed if the distance is closer than 10 cm from the tissue surface. When using the DuploSpray MIS spray device (for minimally invasive/laparoscopic surgery) it should not be sprayed closer than 2 cm. In minimally invasive/laparoscopic procedures, use a pressure regulator device (DuploSpray MIS spray device) that delivers a maximum pressure of no more than 1.5 bar (22 psi) using only carbon dioxide (CO₂) gas. Only use application devices licensed/CE Marked for the administration of TISSEEL.

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.

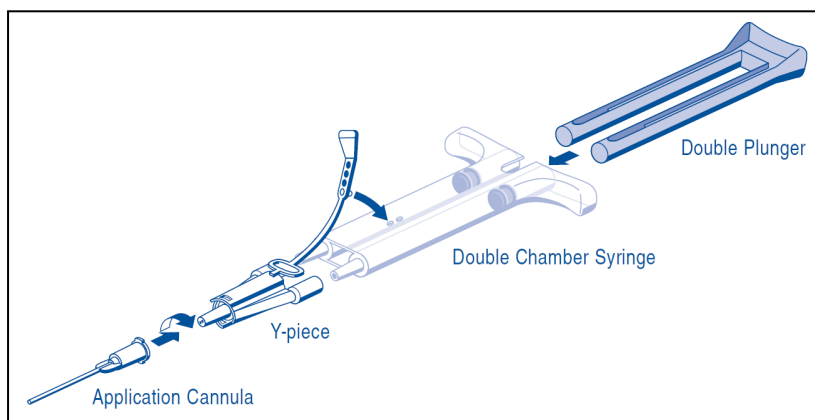
Application beyond the intended area of application should be avoided.

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.

It is strongly recommended that every time TISSEEL is applied to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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 below) 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.

See **INCOMPATIBILITIES**.

4.3 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; and may result in life-threatening thromboembolic complications, can lead to intravascular coagulation, and may increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

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.

Additionally, soft tissue injection of TISSEEL carries the risk of an anaphylactic reaction and/or local tissue damage.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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, the agent that causes Creutzfeldt-Jakob Disease (CJD) in humans. 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. hemolytic anaemia).

All infections thought by a clinician possibly to have been transmitted by TISSEEL should be reported by the clinician or other healthcare provider to Baxter.

Patients should be instructed to consult their clinician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose, followed about two weeks later by a rash and joint pain).

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 repeated exposure occurs within six months. If it is decided to proceed with treatment in such patients, prior administration of antihistamines should be considered.

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 (refer to **ADVERSE EFFECTS**). Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients. Because of the risk of intravascular injection, the product must not be injected into highly vascularised tissue, such as nasal mucosa.

The new formulation of TISSEEL contains synthetic aprotinin. As synthetic aprotinin is structurally identical to bovine aprotinin, the use of TISSEEL in patients with allergies to bovine proteins should be carefully evaluated.

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/or in close proximity to the tissue surface. The risk appears to be higher when TISSEEL sprayed with air, as compared to carbon dioxide (CO₂) and therefore cannot be excluded with TISSEEL when sprayed in open wound surgery.

When using the DuploSpray MIS spray device (for minimally invasive/laparoscopic surgery) it should not be sprayed closer than 2 cm. In minimally invasive/laparoscopic procedures, a pressure regulator device (DuploSpray MIS spray device) that delivers a maximum pressure of no more than 1.5 bar (22 psi) and uses carbon dioxide gas only should be used.

To reduce the risk of a potentially life-threatening gas embolism, 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 (20-25 psi). Do not spray if the distance is 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 CO₂ should be monitored because of the possibility of occurrence of air or gas embolism.

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 to **INCOMPATIBILITIES**).

TISSEEL alone is not indicated for the treatment of severe or brisk arterial or venous bleeding. When used in these situations, TISSEEL is likely to be washed away in the flow of blood before haemostasis can be attained.

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.

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

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 established. There have been rare reports of serious adverse events such as paralysis and other compressive complications possibly related to the use of fibrin sealants in combination with resorbable haemostatic agents.

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

Use in hernia

Nonclinical data indicate that TISSEEL is unlikely to be effective when used alone for mesh fixation to peritoneum (e.g. with an intraperitoneal approach for laparoscopic ventral hernia repair). In such situations TISSEEL should only be used as an adjunct to sutures or staples/tacks.

TISSEEL is not effective when used with Omega 3 fatty acid-containing and non-porous ePTFE meshes. TISSEEL should not be used with these meshes. Furthermore, the efficacy of TISSEEL has not been demonstrated in meshes with other coatings, including with beta glucan.

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.

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 3 mL during a laparotomy for peritoneal adhesions.

Effects on laboratory tests

The effect of this medicine on laboratory tests has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no known interactions between TISSEEL and other drugs. Efficacy has been demonstrated in fully heparinised patients undergoing cardiopulmonary bypass.

Refer to **INCOMPATIBILITIES** for more detailed information on interactions with substances other than drugs.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 fetus.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 flushing, 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.

TISSEEL must not be applied intravascularly (see **CONTRAINDICATIONS**).

Intravascular application can lead to intravascular coagulation, may result in thromboembolic events, and might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

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.

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in clinical practice.

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	Post-procedural pain	Common	7 (1.4%)

Legend: ADR frequency is based upon the following scale: Very Common (>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)

Post-marketing Adverse Reactions

Because adverse reactions are reported voluntarily and the population is of uncertain size, it is not always possible to reliably estimate the frequency of these reactions.

- cardiac disorders: bradycardia, tachycardia
- gastrointestinal disorders: nausea, intestinal obstruction
- general disorders and administration site disorders: hypersensitivity reactions, oedema, pyrexia
- immune system disorders: hypersensitivity (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, seroma
- investigations: drop in blood pressure
- skin and subcutaneous tissue disorders: pruritus, impaired healing
- vascular disorders: haematoma, flush, (severe) hypotension, and thromboembolism, including cerebral artery embolism and venous thrombotic cerebral infarction*, Air embolism**

* as a result of intravascular application into the superior petrosal sinus.

**as with other fibrin sealants life-threatening/fatal air or gas embolism when using devices with pressurized air or gas occurred; this event appears to be related to an inappropriate use of the spray device (e.g. at higher than recommended pressure and in close proximity to the tissue surface).

Class Reactions

Other adverse reactions associated with the fibrin sealant/haemostatic class include: manifestations of hypersensitivity such as application site irritation, chest discomfort, chills, headache, lethargy, restlessness, and vomiting.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

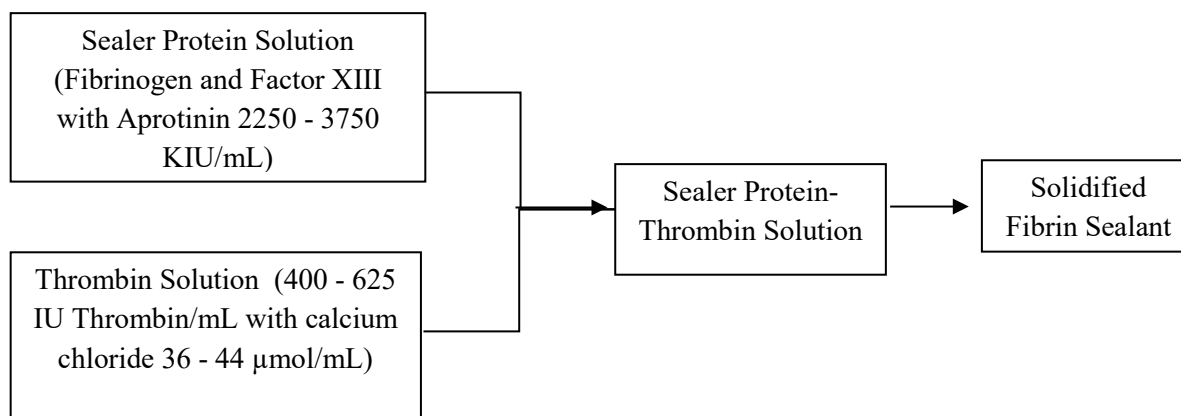
Mechanism of action

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.



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 VH², 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

² 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.

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 HT (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 minutes 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 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	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, open label trial, an earlier formulation of TISSEEL 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	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).

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 TISSEEL 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.

Hernia repair

A prospective, multi-centre, randomized, double-blinded, parallel, controlled clinical trial (Campanelli 2009) involving 325 male subjects was conducted to evaluate the safety and effectiveness of TISSEEL in uncomplicated unilateral or bilateral, direct or indirect primary inguinal hernia using the Lichtenstein technique. Patients were randomized to have mesh fixation either by sutures or by application of TISSEEL.

For the clinically important outcomes of chronic pain and recurrence as well as for pain / no pain the results of the statistical analyses are as follows:

Chronic pain (VAS, in mm (STD))	ITT		p	PP		p
	TISSEEL	Sutures		TISSEEL	Sutures	
6 months	6.35 (14.71)	10.56 (18.12)	0.0052	6.34 (14.79)	10.56 (18.12)	0.0040
12 months	3.87 (11.53)	5.93 (14.75)	0.1134	3.92 (11.60)	5.93 (14.75)	0.1259

No pain (VAS = 0)	ITT		p	PP		p
	TISSEEL	Sutures		TISSEEL	Sutures	
6 months	73.5% (108/147)	59.7% (92/154)	0.0049	73.8% (107/145)	59.7% (92/154)	n.a.
12 months	83.9% (125/149)	76.7% (115/150)	0.1104	83.7% (123/147)	76.7% (115/150)	n.a.

Recurrence	ITT	
	TISSEEL	Sutures
	1/159	2/160

A prospective, single-centre, comparative clinical trial by Hidalgo *et al.* (2005) of 55 subjects aimed to assess the feasibility of TISSEEL for mesh fixation in hernia repair using the Lichtenstein technique. Only subjects who had bilateral inguinal hernias were eligible: sutures were used on the right side and TISSEEL on the left side. The primary efficacy outcomes investigated – recurrence rates at month 12 and chronic pain – did not occur during the study period in either group.

Lau (2005) conducted a single-centre, randomized (1:1), controlled clinical trial to compare the clinical outcomes of simultaneous bilateral endoscopic totally extraperitoneal (TEP) inguinal hernia repair using either an earlier version of TISSEEL or staples for mesh fixation in 93 subjects. Efficacy outcomes were recurrence rate and chronic groin pain. At a median follow-up of 1.2 years there were no incidences of hernia recurrence in either treatment group. The difference in incidence of chronic pain for the 78 subjects assessed at median 2 year follow-up was not significant (TISSEEL 5/38, 13.2% (95% CI 2.5% - 23.9%), and staples 8/40, 20% (95% CI 7.6% - 32.3%)) (p=0.418).

In a prospective single-centre controlled clinical trial by Lovisetto *et al.* (2007), 197 subjects with uni- or bilateral inguinal or femoral hernia underwent laparoscopic transabdominal preperitoneal (TAPP) hernioplasty and were randomized to mesh fixation by either staples (n=98) or TISSEEL (n=99). TISSEEL was applied *via* a laparoscopic catheter.

The primary efficacy outcomes were early postoperative and late neuralgia recorded using a visual analogue scale (VAS): At 1, 3, and 6 months after surgery, the mean VAS score was significantly lower in the TISSEEL group compared with the staples group.

Neuralgia (mean VAS score [mm])	TISSEEL	staples	p
1 month	19	26	< 0.05
3 months	11	23	< 0.001
6 months	11	20	< 0.001
12 months	(8)	(12)	n.a.

Secondary outcomes included:

	TISSEEL	staples	p
Recurrence	1	0	n.a.

A single-centre, prospective, randomized (1:1:1:1), controlled study by Olmi *et al.* (2007) compared pain outcomes in 600 subjects who were treated with Protak (Tyco, Norwalk, CT; group A, n=150 (189 hernias)), EndoANCHOR (Ethicon Endo-Surgery, Inc., Cincinnati, OH; group B, n= 150 (198 hernias)), Endopath Multifeed Stapler (EMS) 10 mm shaft (Ethicon Endo-Surgery, Inc., Cincinnati, OH; group C, n=150 (222 hernias)), or TISSEEL (Baxter Healthcare Corporation, Deerfield, IL; group D, n=150 (222 hernias)) for mesh fixation during laparoscopic TAPP uni- or bilateral inguinal hernia repair. Subjects were followed up to 1 month after surgery for recurrence, postoperative pain on a 10-point VAS, operating time, length of stay, and return to work.

A total of 3 recurrences occurred in the study, all of which occurred in group C (n.s.). The postoperative (24 – 72 hours) pain score in group D (VAS 2) was markedly lower than in groups A (VAS 5-7), B (VAS 4-5), and C (VAS 3-4).

5.2 PHARMACOKINETIC PROPERTIES

Solidified TISSEEL VH S/D 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies of genotoxic potential of TISSEEL have not been performed. Negative results were obtained in bacterial reverse mutation assays (Ames tests) conducted with various components of TISSEEL (sealer protein solution containing bovine aprotinin; synthetic aprotinin; human thrombin solution).

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - **QUALITATIVE AND QUANTITATIVE COMPOSITION**

6.2 INCOMPATIBILITIES

Solutions containing alcohol, iodine or heavy metals will interfere with the product's performance due to denaturation of proteins or other mechanisms. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of TISSEEL.

Oxidised cellulose-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.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Deep frozen TISSEEL has a shelf life of two years when stored at -18°C or colder. The expiry date is stated on the final container and the package.

6.4 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.

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.

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

Special Precautions for Storage

- after thawing, the solutions must not be refrozen or refrigerated
- 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

6.5 NATURE AND CONTENTS OF CONTAINER

Nature of containers:

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

Contents:

Each pack 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).

Set of Devices

Each pack TISSEEL contains a double-sterile set of devices (DUO AST SET or PRIMA) 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 **DOSE AND METHOD OF ADMINISTRATION** – section *Operating instructions*.

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

TISSEEL is available in the following pack sizes:

- TISSEEL 2 mL (containing 1.0 mL of Sealer Protein Solution and 1.0 mL of Thrombin Solution)
- TISSEEL 4 mL (containing 2.0 mL of Sealer Protein Solution and 2.0 mL of Thrombin Solution)
- TISSEEL 10 mL (containing 5.0 mL of Sealer Protein Solution and 5.0 mL of Thrombin Solution).

Package size: 2 mL, 4 mL, 10 mL

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

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

6.7 PHYSICOCHEMICAL PROPERTIES

Fibrinogen:

Chemical Structure: 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 $(A\alpha, B\beta, \gamma)_2$.

Molecular Weight (MW): 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.

CAS No.: 9001-32-5

Thrombin:

Chemical Structure: Thrombin (human origin) is a glycosylated protein, consisting of two polypeptide subunits A and B, covalently linked by one -S-S- bond.

Molecular Weight (MW): about 33 800. The human thrombin subunit A chain is made of 36 amino acids, whilst the B chain contains 259 amino acids.

CAS No.: 9002-04-4

Factor XIII:

Chemical Structure: Factor XIII (human origin), also called blood-coagulation factor XIII, is a tetramer composed of two a-chains and two b-chains which are non-covalently associated.

Molecular Weight (MW): about 190 000 (each of chain weight about 80 000).

CAS No.: 9013-56-3

Aprotinin:

Chemical Structure: Aprotinin (synthetic origin) is a protease inhibitor, a polypeptide consisting of one chain of 58 amino acids, also stabilised by -S-S- bonds

Molecular weight (MW): 6511.5

CAS No.: 9087-70-1

Calcium chloride dihydrate

Molecular formula: $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$

Molecular Weight: 147.01

CAS No.: 10035-04-8

Appearance: a white crystalline powder

Solubility: hygroscopic, freely soluble in water

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled

8 SPONSOR

Baxter Healthcare Pty Ltd
1 Baxter Drive
OLD TOONGABBIE NSW 2146
AUSTRALIA

9 DATE OF FIRST APPROVAL

13 March 2009

10 DATE OF REVISION

April 2019

10.1 Summary table of changes

Section Changed	Summary of new information
ALL	Reformatting to the latest TGA approved form
2, 4.2, 5.1, 6.4 and 6.5	Method or preparation of the new PRIMA Syringe (Section 4.2) and Minor Editorial Changes to sections 2, 5.1, 6.4 and 6.5.