



TISSEEL (Fibrin Sealant)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TISSEEL safely and effectively. See full prescribing information for TISSEEL.

TISSEEL (Fibrin Sealant)

For Topical Use Only

Frozen solution and lyophilized powder for solution for topical application

Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

Dosage and Administration; Method of Application (2.3)	05/2009
Warnings/Precautions; Application Precautions (5.2)	09/2009
Adverse Reactions; Post Marketing (6.3)	11/2009

INDICATIONS AND USAGE

- **Hemostasis:** TISSEEL is a fibrin sealant indicated as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries. TISSEEL is satisfactory for use in fully heparinized patients undergoing cardiopulmonary bypass (1.1)
- **Sealing:** TISSEEL is indicated as an adjunct to prevent leakage from colonic anastomoses following the reversal of temporary colostomies (1.2)

DOSAGE AND ADMINISTRATION

For Topical Use Only. Do Not Inject (2)

TISSEEL Kit (Freeze-Dried) requires reconstitution prior to use (2.1)
 TISSEEL Pre-filled Syringe (Frozen) requires thawing prior to use (2.2)
 Apply TISSEEL as a thin layer (2.3, 5.2)
 Vials and pre-filled syringes are for single use only. Discard unused contents (2.3)

DOSAGE FORMS AND STRENGTHS

TISSEEL Kit (Freeze-Dried) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with and without the DUPLOJECT System (3.1).
 TISSEEL Pre-filled Syringe (Frozen) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with the DUO Set (3.1).

CONTRAINDICATIONS

- Do not inject directly into the circulatory system (4.1, 5.3)
- Do not use in individuals with a known hypersensitivity to aprotinin (4.2, 5.1, 6.1)
- Do not use for the treatment of severe or brisk arterial bleeding (4.3)

WARNINGS AND PRECAUTIONS

- Apply only as thin layer (2, 5.2)
- 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 surface of the tissue (5.2)
- Exposure to solutions containing alcohol, iodine or heavy metals may cause TISSEEL to be denatured (5.2)
- Safety has not been evaluated in neurosurgical procedures (5.4)
- The safety and effectiveness of the combined use of TISSEEL with other biocompatible materials has not been evaluated in controlled clinical trials (5.4, 6.3)
- This product is made from pooled human plasma which may, theoretically, contain infectious agents (5.5)

ADVERSE REACTIONS

Anaphylactic and hypersensitivity reactions have been reported. No adverse events of this type were reported during clinical trials (5.1, 6.1, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Oxycellulose containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2010

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE

- 1.1 Hemostasis
- 1.2 Sealing

2 DOSAGE AND ADMINISTRATION

- 2.1 Preparation of TISSEEL Kit (Freeze-Dried)
- 2.2 Preparation of TISSEEL Pre-Filled Syringe (Frozen)
- 2.3 Method of Application

3 DOSAGE FORMS AND STRENGTHS

- 3.1 Presentations and Pack Sizes
- 3.2 Package Contents

4 CONTRAINDICATIONS

- 4.1 Intravascular Application
- 4.2 Aprotinin Hypersensitivity
- 4.3 Arterial Bleeding

5 WARNINGS/PRECAUTIONS

- 5.1 Hypersensitivity/Allergic/Anaphylactic Reactions
- 5.2 Application Precautions
- 5.3 Use in Cardiopulmonary Surgery
- 5.4 Use in Neurosurgical Procedures
- 5.5 Infection Risk from Human Plasma

6 ADVERSE REACTIONS

- 6.1 Overall Adverse Reactions
- 6.2 Clinical Trials Experience
- 6.3 Post Marketing

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Lactating Women
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Other Clinical Pharmacology Information

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Cardiac Surgery
- 14.2 Cardiac Reoperations
- 14.3 Splenectomy
- 14.4 Colostomy Closure

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

1.1 Hemostasis: TISSEEL is indicated for use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical. TISSEEL is a satisfactory hemostatic agent in fully heparinized patients undergoing cardiopulmonary bypass.

1.2 Sealing: TISSEEL is indicated as an adjunct to prevent leakage from colonic anastomoses following the reversal of temporary colostomies.

2 DOSAGE AND ADMINISTRATION

FOR TOPICAL USE ONLY – DO NOT INJECT.

The required dose of TISSEEL depends on the size of the surface to be covered. The approximate surface areas covered by each package size of TISSEEL are listed in the following table:

Table 1.

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

2.1 Preparation of TISSEEL Kit (Freeze-Dried)

During preparation of TISSEEL Kit:

DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C
DO NOT REFRIGERATE AFTER RECONSTITUTION

Do not use iodine or heavy metal containing preparations such as betadine for disinfection of vial stoppers. Allow alcohol-based disinfectants to evaporate before puncturing stopper.

Use separate syringes for reconstituting Sealer Protein and Thrombin solutions and for application to prevent premature clotting.

After reconstitution, the product must be used within 4 hours.

TISSEEL Kit contains the following substances in four separate vials:

- Sealer Protein Concentrate (Human)
- Fibrinolysis Inhibitor Solution (Synthetic)
- Thrombin (Human)
- Calcium Chloride Solution

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

Prewarming TISSEEL Kit with FIBRINOTHERM

If a FIBRINOTHERM device is not available, contact Baxter (1-800-423-2090) for assistance. See FIBRINOTHERM manual for complete operating instructions.

1. Plug the FIBRINOTHERM Heating and Stirring Device into an electrical socket and activate the warmer (amber switch). Ensure that the stirring mechanism of the FIBRINOTHERM device is initially switched off (green switch).
2. Place all four vials from the TISSEEL Kit into the prewarmed wells of the FIBRINOTHERM, using the appropriately sized adapter rings, and allow the vials to warm for up to 5 minutes (room temperature product may take less time).

Preparation of Sealer Protein Solution with FIBRINOTHERM

1. Remove the flip-off caps from the vial containing the Sealer Protein Concentrate and the vial containing the Fibrinolysis Inhibitor Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry.
2. Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein Concentrate using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with TISSEEL (see directions provided with the device system for specific reconstitution instructions). Gently swirl the vial to ensure that the freeze-dried material is completely soaked.
3. Place the vial into the largest opening of the FIBRINOTHERM device with the appropriate adaptor. Switch on the stirrer (green switch) and allow the vial contents to stir until all Sealer Protein Concentrate is dissolved.
4. Reconstitution of the freeze-dried Sealer Protein Concentrate is complete as soon as no undissolved particles are visible. Otherwise, return the vial to the FIBRINOTHERM device and agitate for a few more minutes until the solution appears homogeneous.

Notes:

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

Preparation of Thrombin Solution with FIBRINOTHERM

1. Remove the flip-off caps from the vial containing Thrombin and the vial containing Calcium Chloride Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry.
2. Transfer the contents of the vial with Calcium Chloride Solution into the vial containing the freeze-dried Thrombin using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with TISSEEL (see directions provided with the device system for specific reconstitution instructions).
3. Swirl briefly.
4. Place the vial into the adapted opening of the FIBRINOTHERM device.
5. Reconstitution of Thrombin is complete when all of the Thrombin concentrate is dissolved.
6. Keep the Thrombin Solution at 37°C until used.

Transferring to the Sterile Field

For transfer of the Sealer Protein Solution and the Thrombin Solution to the sterile field, the scrub nurse should withdraw the solutions while the circulating nurse holds the non-sterile vials. The solutions should be withdrawn slowly by firm constant aspiration to reduce the risk of large air bubbles.

See *DOSAGE AND ADMINISTRATION, Method of Application (2.3)*.

2.2 Preparation of TISSEEL Pre-Filled Syringe (Frozen)

During preparation of TISSEEL (frozen):

DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C

DO NOT MICROWAVE

DO NOT REFRIGERATE OR RE-FREEZE

Do not use TISSEEL (frozen) until it is completely thawed and warmed (liquid consistency).

Do not remove the protective syringe cap until use.

TISSEEL (Fibrin Sealant)

After thawing, the product must be stored between 15°C and 37°C (room temperature and 37°C).

Thaw pre-filled syringes in one of the three following options:

Option 1 – Thawing on the sterile field using a water bath

33°C to 37°C sterile water bath – transfer DUO set and the inner pouch to the sterile field, remove pre-filled syringe from inner pouch and place directly into sterile water bath. Ensure the contents of the pre-filled 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)
2 mL	5 minutes
4 mL	5 minutes
10 mL	12 minutes

Option 2 – Thawing off the sterile field using a water bath

33°C to 37°C non-sterile water bath in two pouches – maintain the pre-filled syringe 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 with pre-filled 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)
2 mL	30 minutes
4 mL	40 minutes
10 mL	80 minutes

Option 3 – Thawing off the sterile field using an incubator

33°C to 37°C incubator in pouches – maintain the pre-filled syringe in both pouches and place into an incubator for appropriate time. Remove from incubator after thawing and transfer inner pouch with pre-filled 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)
2 mL	40 minutes
4 mL	85 minutes
10 mL	105 minutes

Keep the product 33 – 37°C until needed.

See **DOSAGE AND ADMINISTRATION, Method of Application (2.3)**.

2.3 Method of Application

Application of TISSEEL must be completed within 4 hours after reconstitution of the freeze-dried kit or opening the pre-filled frozen syringes. Ensure TISSEEL is warmed to 33 – 37°C prior to application.

Vials and pre-filled syringes are for single use only. Discard any unused product.

The wound surface should be as dry as possible before application.

Immediately before application, expel and discard the first several drops from the application cannula to ensure adequate mixing of the Sealer Protein and Thrombin solutions in cases where very small volumes (1 – 2 drops) of product are administered.

To prevent adherence, wet gloves with normal saline before product contact.

Apply TISSEEL as a thin layer. The initial amount of the product to be applied should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

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.

TISSEEL Kit (Freeze-Dried)

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

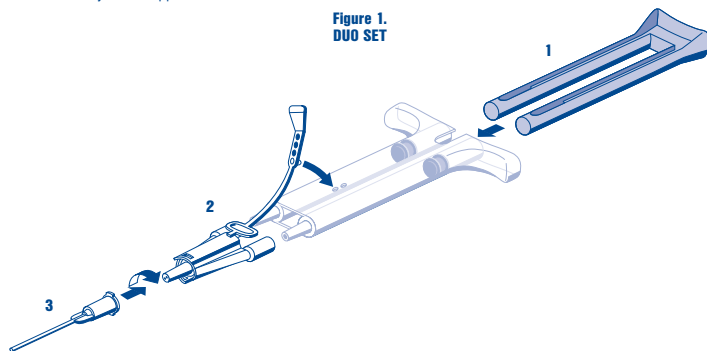
TISSEEL Pre-filled Syringe (Frozen)

Apply pre-filled TISSEEL using the DUO Set accessory devices provided with the product or an equivalent delivery device cleared by FDA for use with TISSEEL.

DUO Set Instructions (see Figure 1 below):

1. Insert plunger into syringe barrel.
2. Firmly connect the two syringe nozzles to the joining piece and secure it by fastening the tether strap to the syringe.
3. Fit an application cannula to the joining piece. If application of TISSEEL is interrupted, replace the cannula immediately before application is resumed.

Figure 1.
DUO SET



3 DOSAGE FORMS AND STRENGTHS

3.1 Presentations and Pack Sizes

TISSEEL Kit (Freeze-Dried) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with and without the DUPLOJECT Preparation and Application System.

TISSEEL Pre-filled Syringe (Frozen) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with the DUO Set.

3.2 Package Contents

TISSEEL Kit (Freeze-Dried) and TISSEEL Kit (Freeze-Dried) with DUPLOJECT System

1. Sealer Protein Concentrate (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile
2. Fibrinolysis Inhibitor Solution (Synthetic), Sterile
3. Thrombin (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile
4. Calcium Chloride Solution, Sterile
5. DUPLOJECT Preparation and Application System (if indicated on the carton)

TISSEEL Pre-Filled Syringe (Frozen) with DUO Set

1. (1) Sealer Protein Solution, Vapor Heated, Solvent/Detergent Treated, Sterile
2. (2) Thrombin Solution, Vapor Heated, Solvent/Detergent Treated, Sterile
3. Sterile accessory devices (DUO Set: 1 plunger, 2 joining pieces and 4 application cannulas) are included with each pre-filled syringe

TISSEEL (Fibrin Sealant)

The reconstituted solution or pre-filled syringe contains:

Sealer Protein Solution

Total protein:	96 – 125 mg/mL
Fibrinogen:	67 – 106 mg/mL
Fibrinolysis Inhibitor (Synthetic):	2250 – 3750 KIU/mL
Other ingredients include: human albumin, tri-sodium citrate, histidine, niacinamide, polysorbate 80 and water for injection (WFI).	

Thrombin Solution

Thrombin (Human):	400 – 625 units/mL*
Calcium Chloride:	36 – 44 µmol/mL
Other ingredients include: human albumin, sodium chloride and water for injection (WFI).	

* The potency expressed in units is determined using a clotting assay against an internal reference standard for potency that has been calibrated against the World Health Organization (WHO) Second International Standard for Thrombin, 01/580. Therefore, a unit (U) is equivalent to an International Unit (IU).

4 CONTRAINDICATIONS

4.1 IntraVascular Application

Do not inject TISSEEL directly into the circulatory system. Intravascular application of TISSEEL may result in life-threatening thromboembolic events (see WARNINGS/PRECAUTIONS, Use in Cardiopulmonary Surgery (5.3) and ADVERSE REACTIONS, Post Marketing (6.3)).

4.2 Aprotinin Hypersensitivity

Do not use TISSEEL in individuals with a known hypersensitivity to aprotinin (see WARNINGS/PRECAUTIONS, Hypersensitivity/Allergic/Anaphylactic Reactions (5.1) and ADVERSE REACTIONS, Overall Adverse Reactions (6.1)).

4.3 Arterial Bleeding

Do not use TISSEEL for treatment of severe or brisk arterial bleeding. In these situations, TISSEEL will be washed away in the flow of blood before hemostasis can be attained.

5 WARNINGS/PRECAUTIONS

5.1 Hypersensitivity/Allergic/Anaphylactic Reactions

Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of TISSEEL. Cases (<1/10,000) have been reported in post marketing experience with Baxter's fibrin sealant (see ADVERSE REACTIONS, Post Marketing (6.3)). In specific cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if TISSEEL is applied repeatedly over time or in the same setting, or if systemic aprotinin has been administered previously. Even if the first treatment was well tolerated, this may not exclude the occurrence of an allergic reaction after a subsequent administration of TISSEEL or systemic aprotinin. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock. Such reactions may also occur in patients receiving TISSEEL for the first time.

Discontinue administration of TISSEEL in the event of hypersensitivity reactions. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

5.2 Application Precautions

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 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.

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 CO₂ 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. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before the application of TISSEEL.

5.3 Use in Cardiopulmonary Surgery

Caution should be exercised to minimize the risk of inadvertent intravascular application when using TISSEEL in cardiopulmonary bypass surgeries (see CONTRAINDICATIONS, Intravascular Application (4.1) and ADVERSE REACTIONS, Post Marketing (6.3)).

5.4 Use in 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, and its use in this setting is not approved by FDA (see ADVERSE REACTIONS, Post Marketing (6.3) and DRUG INTERACTIONS (7)).

5.5 Infection Risk from Human Plasma

TISSEEL is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses (see CLINICAL PHARMACOLOGY, Other Clinical Pharmacology Information (12.4)). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, telephone # 1-866-888-2472.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions

Hypersensitivity/Allergic/Anaphylactic Reactions: Hypersensitivity or allergic/anaphylactoid reactions may occur. In isolated cases, these reactions have progressed to severe anaphylaxis (see WARNINGS/PRECAUTIONS, Hypersensitivity/Allergic/Anaphylactic Reactions (5.1)). No adverse events of this type were reported during clinical trials.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely 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 practice.

Increased D-Dimer levels have been observed during a clinical study in cardiovascular surgery (see CLINICAL STUDIES (14)), but did not exceed values reported in the literature occurring after this type of surgery. Postoperatively increased D-Dimers may result at least partly from the degradation of Fibrin Sealant.

6.3 Post Marketing

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.

There have been reports of the following adverse reactions:

Immune system disorders: hypersensitivity, anaphylactic responses

Cardiac disorders: bradycardia, tachycardia, hypotension, thromboembolic complications

Respiratory, thoracic and mediastinal disorders: dyspnea

Gastrointestinal disorders: nausea

Skin and subcutaneous tissue disorders: urticaria, pruritus

General disorders and administration site conditions: flushing

Air embolism associated with misapplication of fibrin sealant using the spray device, Class Effect: A post marketing fatality was reported in association with the use of another fibrin sealant when applied using a spray device. The case involved an attempt to stop active bleeding by applying the fibrin sealant using a spray device attached to a wall unit at a higher than recommended pressure for the spray device. In addition, the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant. The patient suffered a fatal air embolism.

There have been reports of serious adverse events such as paralysis and other compressive complications possibly related to the use of fibrin sealants in combination with resorbable hemostatic agents. There have also been reports of fatalities following the misadministration of topical thrombin (see WARNINGS/ PRECAUTIONS, Use in Neurosurgical Procedures (5.4)).

7 DRUG INTERACTIONS

Oxycellulose containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials.
No formal interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Pregnancy Category C**

Animal reproduction studies have not been conducted with TISSEEL. It is also not known whether TISSEEL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection). TISSEEL should be given to a pregnant woman only if clearly needed.

8.3 Lactating Women

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TISSEEL is administered to a lactating woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

In a Phase 3 clinical study of TISSEEL 71 out of 144 subjects were 65 and over (see *CLINICAL STUDIES* (14)). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

TISSEEL [Fibrin Sealant], Vapor Heated, Solvent Detergent Treated, (TISSEEL) is a two-component fibrin sealant made from pooled human plasma. When combined, the two components, Sealer Protein (Human) and Thrombin (Human), mimic the final stage of the blood coagulation cascade.

Sealer Protein (Human)

Sealer Protein (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Sealer Protein (Human) is provided either as a freeze-dried powder [Sealer Protein Concentrate (Human)] for reconstitution with Fibrinolysis Inhibitor Solution (Synthetic) or as a finished frozen solution pre-filled into one side of a dual-chambered syringe (1). The active ingredient in Sealer Protein (Human) is fibrinogen. A Fibrinolysis Inhibitor, Aprotinin (Synthetic) is included in the Sealer Protein (Human) component to delay fibrinolysis. Aprotinin (Synthetic) is manufactured by solid phase synthesis from materials completely of non-human/non-animal origin.

To obtain Sealer Protein (Human), cryoprecipitate derived from the plasma is washed, dissolved in buffer solution, solvent/detergent treated, vapor heat treated, sterile filtered and either freeze-dried in vials or frozen in pre-filled syringes.

Thrombin (Human)

Thrombin (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Thrombin (Human) is also provided either as a freeze-dried powder for reconstitution with Calcium Chloride Solution or as a finished frozen solution pre-filled into one side of a dual-chambered syringe (2).

Thrombin is prepared from plasma through a series of separation and filtration steps followed by incubation of the solution with calcium chloride to activate prothrombin to thrombin. The solution subsequently undergoes ultra/diafiltration, vapor heat treatment, solvent/detergent treatment, sterile filtration and is either freeze-dried in vials or frozen in pre-filled syringes.

Sealer Protein (Human) and Thrombin (Human) are made from pooled human plasma collected at US licensed collection centers. The vapor heat and solvent/detergent treatment steps used in the manufacturing process have been shown to be capable of significant viral reduction. No procedure, however, has been shown to be completely effective in removing viral infectivity from derivatives of human plasma (see *CLINICAL PHARMACOLOGY, Other Clinical Pharmacology Information* (12.4) and *WARNINGS/PRECAUTIONS, Infection Risk from Human Plasma* (5.5)).

See *DOSAGE FORMS AND STRENGTHS* (3).

12 CLINICAL PHARMACOLOGY**12.1 Mechanism of Action**

Upon mixing Sealer Protein (Human) and Thrombin (Human), soluble fibrinogen is transformed into fibrin, forming a rubber-like mass that adheres to the wound surface and achieves hemostasis and sealing or gluing of tissues.

12.2 Pharmacodynamics

Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin (see *Pharmacokinetics* (12.3)).

Fibrinolysis Inhibitor, Aprotinin (Synthetic), is a polyvalent protease inhibitor that prevents premature degradation of fibrin. Free Aprotinin and its metabolites have a half-life of 30 to 60 minutes and are eliminated by the kidney. Preclinical studies with different fibrin sealant preparations simulating the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of aprotinin in the product formulation increases resistance of the fibrin sealant clot to degradation in a fibrinolytic environment.

12.3 Pharmacokinetics

Pharmacokinetic studies were not conducted. Because TISSEEL is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.

12.4 Other Clinical Pharmacology Information**Viral Clearance**

The manufacturing procedure for TISSEEL includes processing steps designed to further reduce the risk of viral transmission. In particular, vapor heating and solvent/detergent treatment processes are included in the manufacturing of Sealer Protein Concentrate and Thrombin. Validation studies were conducted using samples drawn from manufacturing intermediates for each of the two human plasma derived components. These samples were spiked with stock virus suspensions of known titers followed by further processing under conditions equivalent to those in the respective manufacturing steps.

The virus reduction factors (expressed as log₁₀) of manufacturing steps for each of the viruses tested are shown in Table 2.

Table 2.

Reduction Factors for Virus Removal and/or Inactivation Sealer Protein Component					
Manufacturing Step	Mean Reduction Factors [log ₁₀] of Virus Tested				
	HIV-1	HAV	BVDV	PRV	MMV
Early Manufacturing Steps	n.d.	n.d.	n.d.	n.d.	2.7
Solvent/Detergent Treatment	> 5.3	n.d.	> 5.7	> 5.9	n.d.
Vapor Heat Treatment	> 5.5	>5.6	> 5.7	> 6.7	1.2
Overall Reduction Factor (ORF)	>10.8	>5.6	>11.4	>12.6	3.9
Reduction Factors for Virus Removal and/or Inactivation Thrombin Component					
Manufacturing Step	Mean Reduction Factors [log ₁₀] of Virus Tested				
	HIV-1	HAV	BVDV	PRV	MMV
Thrombin Precursor Mass Capture	3.2	1.5	1.8	2.5	1.2
Vapor Heat Treatment	> 5.5	> 4.9	> 5.3	> 6.7	1.0
Solvent/Detergent Treatment	> 5.3	n.d.	> 5.5	> 6.4	n.d.
Ion Exchange Chromatography	n.d.	n.d.	n.d.	n.d.	3.6
Overall Reduction Factor (ORF)	>14.0	>6.4	>12.6	>15.6	5.8

n.d. = not determined

HIV-1: Human immunodeficiency virus 1; **HAV:** Hepatitis A virus; **BVDV:** Bovine viral diarrhea virus, a model for Hepatitis C virus; **PRV:** Pseudorabies virus, a model for enveloped DNA viruses, among those Hepatitis B virus; **MMV:** Mice minute virus, a model for B19V.

In addition, Human Parvovirus B19V was used to investigate the upstream Thrombin precursor mass capture step, the Sealer Protein early manufacturing steps and the Thrombin and Sealer Protein vapor heating steps. Using quantitative PCR assays, the estimated log reduction factors obtained were 1.7 and 3.4 for the Thrombin precursor mass capture step and Sealer Protein early manufacturing steps and >4 / 1.0 for the Thrombin / Sealer Protein vapor heating steps, respectively.

13 NONCLINICAL TOXICOLOGY**13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility**

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

14 CLINICAL STUDIES**14.1 Cardiac Surgery**

TISSEEL was evaluated in a prospective, parallel design, randomized (1:1), double-blind, multicenter clinical study against an earlier formulation of the product, TISSEEL VH, in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) and median sternotomy. Patients were treated with TISSEEL or the control product only when hemostasis was not achieved by conventional surgical methods. For the endpoint, hemostasis achieved at the primary treatment site within 5 minutes of treatment and maintained until closure of the surgical wound, TISSEEL 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.

Table 3.

Hemostasis within 5 minutes and maintained until surgical closure		
	TISSEEL	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%)

14.2 Cardiac Reoperations

An earlier formulation of TISSEEL was evaluated in an open-label crossover study against control topical hemostatic agents in 489 patients undergoing cardiovascular reoperation or re-sternotomy at 11 institutions. Patients were randomized to TISSEEL or control hemostatic agents when a topical hemostatic was needed at the conclusion of surgery and after all attempts at surgical hemostasis. Patients were crossed to the alternative therapy if bleeding continued after the 5 minute endpoint. At 10 centers, TISSEEL was used after administration of protamine sulfate. At one site, TISSEEL could be used before administration of protamine sulfate. 365 of the 489 patients developed bleeding episodes requiring treatment. For the endpoint (successful hemostasis at 5 minutes), TISSEEL was statistically significantly superior to control topical hemostatic agents in these patients. Similarly, absolute time to cessation of bleeding was statistically significantly shorter for TISSEEL than for control topical hemostatic agents (p<0.0001, Gehan-Wilcoxon test, two sided).

Table 4.

Hemostasis within 5 minutes		
TISSEEL	Control Topical Hemostatic Agent	
82.4% (159/193)	44.5% (76/172)	
Pearson χ^2 two sided; p <0.0001; intent-to-treat analysis		

14.3 Splenectomy

In a single center, 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 hemostatic maneuvers (Refer to Table 5). TISSEEL did not result in 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).

Table 5.

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

14.4 Colostomy Closure

In a single center, prospective open label study of 120 patients randomized to standard of care (59 patients) or standard of care plus fibrin sealant (61 patients) for elective colostomy closure after temporary colostomy placement for treatment of traumatic injury to the colon, the earlier version of TISSEEL plus standard of care was also shown to be 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

TISSEEL is supplied in the following pack sizes and presentations:

Table 6.

Pack Size	NDC Number		
	TISSEEL Kit (Freeze-Dried)	TISSEEL Kit (Freeze-Dried) with DUPLOJECT System	TISSEEL Pre-Filled Syringe (Frozen) with DUO Set
2 mL	0944-4201-03	0944-4201-04	0944-8402-02
4 mL	0944-4201-07	0944-4201-08	0944-8402-04
10 mL	0944-4201-11	0944-4201-12	0944-8402-10

Storage**TISSEEL Kit (Freeze-Dried)**

Store at 2°C to 25°C. Avoid freezing.

TISSEEL Pre-filled Syringe (Frozen)

Long term: Store at ≤ -20°C.

Short term: Thawed, unopened pouches may be stored for up to 48 hours at room temperature (15 – 25°C) after removal from the freezer. **Do not refrigerate or re-freeze.**

After reconstitution of the solutions of the TISSEEL Kit and after opening the TISSEEL (Frozen) package the Fibrin Sealant must be used within 4 hours.

Do not use after the expiration date. Discard if packaging of any components is damaged.

17 PATIENT COUNSELING INFORMATION

Because this product is made from human plasma, the physician should discuss the risks and benefits of this product with the patient.

Patients should be instructed to consult their physician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose) followed about two weeks later by a rash and joint pain (see *USE IN SPECIFIC POPULATIONS, Pregnancy* (8.1)).

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This product, or its use, may be covered by one or more US Patents including US Patent Nos. 4,640,834, 5,962,405 and 5,714,370, in addition to others including patents pending.

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