

## 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](http://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.

## TISSEEL [Fibrin Sealant]

### 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 <sup>2</sup>	100 cm <sup>2</sup>	2 mL
16 cm <sup>2</sup>	200 cm <sup>2</sup>	4 mL
40 cm <sup>2</sup>	500 cm <sup>2</sup>	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.

## TISSEEL [Fibrin Sealant]

- 70 2. Transfer the contents of the vial with Calcium Chloride Solution into the vial containing the freeze-dried Thrombin using the sterile
- 71 reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for
- 72 use with TISSEEL (see directions provided with the device system for specific reconstitution instructions).
- 73 3. Swirl briefly.
- 74 4. Place the vial into the adapted opening of the FIBRINOTHERM device.
- 75 5. Reconstitution of Thrombin is complete when all of the Thrombin concentrate is dissolved.
- 76 6. Keep the Thrombin Solution at 37°C until used.

### Transferring to the Sterile Field

78 For transfer of the Sealer Protein Solution and the Thrombin Solution to the sterile field, the scrub nurse should withdraw the solutions while the

79 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.

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

## 2.2 Preparation of TISSEEL Pre-Filled Syringe (Frozen)

### During preparation of TISSEEL (frozen):

88 **DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C**

89 **DO NOT MICROWAVE**

90 **DO NOT REFRIGERATE OR RE-FREEZE**

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

93 Do not remove the protective syringe cap until use.

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

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

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

100 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

101 into sterile water bath. Ensure the contents of the pre-filled syringe are completely immersed under the water.

103 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

107 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

108 appropriate time. Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and

109 transfer inner pouch with pre-filled syringe onto the sterile field.

111 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

114 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

115 incubator after thawing and transfer inner pouch with pre-filled syringe onto the sterile field.

117 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

118 Keep the product 33-37°C until needed.

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

## 2.3 Method of Application

123 Application of TISSEEL must be completed within 4 hours after reconstitution of the freeze-dried kit or opening the pre-filled frozen syringes. Ensure

124 TISSEEL is warmed to 33 – 37°C prior to application.

## TISSEEL [Fibrin Sealant]

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

127  
128 The wound surface should be as dry as possible before application.

129  
130 Immediately before application, expel and discard the first several drops from the application cannula to ensure adequate mixing of the Sealer Protein  
131 and Thrombin solutions in cases where very small volumes (1-2 drops) of product are administered.

132  
133 To prevent adherence, wet gloves with normal saline before product contact.

134  
135 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  
136 application can be repeated, if necessary.

137  
138 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  
139 TISSEEL adheres firmly to the surrounding tissue.

### TISSEEL Kit (Freeze-Dried)

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

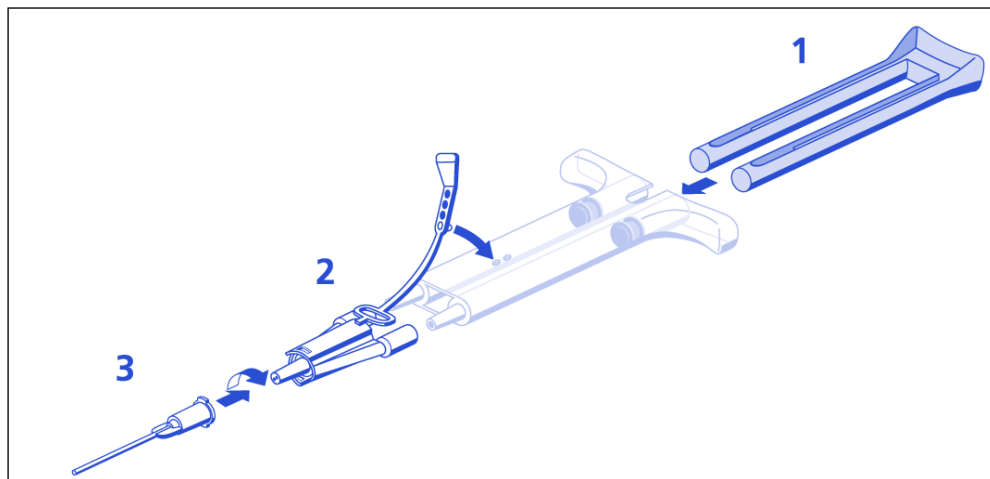
### TISSEEL Pre-filled Syringe (Frozen)

146 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  
147 TISSEEL.

148 DUO Set Instructions (see Figure 1 below):

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

153  
154 **Figure 1.**  
**DUO SET**



## 3 DOSAGE FORMS AND STRENGTHS

### 3.1 Presentations and Pack Sizes

176 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  
177 Application System.

178 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

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

183 1. Sealer Protein Concentrate (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile

184 2. Fibrinolysis Inhibitor Solution (Synthetic), Sterile

185 3. Thrombin (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile

186 4. Calcium Chloride Solution, Sterile

187 5. DUPLOJECT Preparation and Application System (if indicated on the carton)

188  
189 TISSEEL Pre-Filled Syringe (Frozen) with DUO Set

190 1. (1) Sealer Protein Solution, Vapor Heated, Solvent/Detergent Treated, Sterile

191 2. (2) Thrombin Solution, Vapor Heated, Solvent/Detergent Treated, Sterile

192 3. Sterile accessory devices (DUO Set: 1 plunger, 2 joining pieces and 4 application cannulas) are included with each pre-filled syringe

193  
194 The reconstituted solution or pre-filled syringe contains:

195  
196 Sealer Protein Solution  
197 Total protein: 96 – 125 mg/mL  
198 Fibrinogen: 67 – 106 mg/mL  
199 Fibrinolysis Inhibitor (Synthetic): 2250 – 3750 KIU/mL

## **TISSEEL [Fibrin Sealant]**

200 Other ingredients include: human albumin, tri-sodium citrate, histidine, niacinamide, polysorbate 80 and water for injection (WFI).

201  
202 Thrombin Solution

203 Thrombin (Human): 400 – 625 units/mL\*

204 Calcium Chloride: 36 – 44 µmol/mL

205 Other ingredients include: human albumin, sodium chloride and water for injection (WFI).

206

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

210

### **4 CONTRAINDICATIONS**

#### **4.1 Intravascular Application**

213 **Do not inject TISSEEL directly into the circulatory system. Intravascular application of TISSEEL may result in life-threatening**  
214 **thromboembolic events (see WARNINGS/PRECAUTIONS, Use in Cardiopulmonary Surgery (5.3) and ADVERSE REACTIONS, Post Marketing**  
215 **(6.3)).**

216

#### **4.2 Aprotinin Hypersensitivity**

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

220

#### **4.3 Arterial Bleeding**

222 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  
223 hemostasis can be attained.

224

### **5 WARNINGS/PRECAUTIONS**

#### **5.1 Hypersensitivity/Allergic/Anaphylactic Reactions**

227 Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of TISSEEL. Cases (<1/10,000) have been reported in post marketing  
228 experience with Baxter's fibrin sealant (see ADVERSE REACTIONS, Post Marketing (6.3)). In specific cases, these reactions have progressed to severe  
229 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  
230 administered previously. Even if the first treatment was well tolerated, this may not exclude the occurrence of an allergic reaction after a subsequent  
231 administration of TISSEEL or systemic aprotinin. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea,  
232 drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock. Such reactions may also occur in patients  
233 receiving TISSEEL for the first time.

234

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

237

238

#### **5.2 Application Precautions**

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

241

242 Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. This event appears to be  
243 related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

244

245 When applying TISSEEL using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer.  
246 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  
247 device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying  
248 TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO<sub>2</sub> should be monitored because of the possibility of occurrence of air or  
249 gas embolism.

250

251 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  
252 the wound area, the area must be thoroughly rinsed before the application of TISSEEL.

253

#### **5.3 Use in Cardiopulmonary Surgery**

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

257

#### **5.4 Use in Neurosurgical Procedures**

259 The safety and effectiveness of TISSEEL used alone or in combination with biocompatible carriers in neurosurgical procedures or other surgeries  
260 involving confined spaces have not been evaluated, and its use in this setting is not approved by FDA (see ADVERSE REACTIONS, Post Marketing  
261 (6.3) and DRUG INTERACTIONS (7)).

262

#### **5.5 Infection Risk from Human Plasma**

264 TISSEEL is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The  
265 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  
266 the presence of certain current virus infections, and by inactivating and removing certain viruses (see CLINICAL PHARMACOLOGY, Other Clinical  
267 Pharmacology Information (12.4)). Despite these measures, such products can still potentially transmit disease. Because this product is made from  
268 human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL  
269 infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to  
270 Baxter Healthcare Corporation, telephone # 1-866-888-2472.

271

## TISSEEL [Fibrin Sealant]

### 272 **6 ADVERSE REACTIONS**

#### 273 **6.1 Overall Adverse Reactions**

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

277

#### 278 **6.2 Clinical Trials Experience**

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

281

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

285

286

#### 287 **6.3 Post Marketing**

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

290

291 There have been reports of the following adverse reactions:

292

293 **Immune system disorders:** hypersensitivity, anaphylactic responses

294 **Cardiac disorders:** bradycardia, tachycardia, hypotension, thromboembolic complications

295 **Respiratory, thoracic and mediastinal disorders:** dyspnea

296 **Gastrointestinal disorders:** nausea

297 **Skin and subcutaneous tissue disorders:** urticaria, pruritus

298 **General disorders and administration site conditions:** flushing

299

300 Air embolism associated with misapplication of fibrin sealant using the spray device, Class Effect: A post marketing fatality was reported in association  
301 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  
302 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  
303 placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant. The patient  
304 suffered a fatal air embolism.

305

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

309

### 310 **7 DRUG INTERACTIONS**

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

312 No formal interaction studies have been performed.

313

### 314 **8 USE IN SPECIFIC POPULATIONS**

#### 315 **8.1 Pregnancy**

##### 316 **Pregnancy Category C**

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

320

#### 321 **8.3 Lactating Women**

322 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  
323 TISSEEL is administered to a lactating woman.

324

#### 325 **8.4 Pediatric Use**

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

327

#### 328 **8.5 Geriatric Use**

329 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  
330 effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in  
331 responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

332

### 333 **11 DESCRIPTION**

334 TISSEEL [Fibrin Sealant], Vapor Heated, Solvent Detergent Treated, (TISSEEL) is a two-component fibrin sealant made from pooled human plasma.

335 When combined, the two components, Sealer Protein (Human) and Thrombin (Human), mimic the final stage of the blood coagulation cascade.

336

#### 337 **Sealer Protein (Human)**

338 Sealer Protein (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Sealer  
339 Protein (Human) is provided either as a freeze-dried powder [Sealer Protein Concentrate (Human)] for reconstitution with Fibrinolysis Inhibitor Solution  
340 (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  
341 fibrinogen. A Fibrinolysis Inhibitor, Aprotinin (Synthetic) is included in the Sealer Protein (Human) component to delay fibrinolysis. Aprotinin (Synthetic) is  
342 manufactured by solid phase synthesis from materials completely of non-human/non-animal origin.

343

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

346

**TISSEEL [Fibrin Sealant]**

**347 Thrombin (Human)**

348 Thrombin (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Thrombin  
349 (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  
350 one side of a dual-chambered syringe (2).

351  
352 Thrombin is prepared from plasma through a series of separation and filtration steps followed by incubation of the solution with calcium chloride to  
353 activate prothrombin to thrombin. The solution subsequently undergoes ultra/diafiltration, vapor heat treatment, solvent/detergent treatment, sterile  
354 filtration and is either freeze-dried in vials or frozen in pre-filled syringes.

355  
356 Sealer Protein (Human) and Thrombin (Human) are made from pooled human plasma collected at US licensed collection centers. The vapor heat and  
357 solvent/detergent treatment steps used in the manufacturing process have been shown to be capable of significant viral reduction. No procedure,  
358 however, has been shown to be completely effective in removing viral infectivity from derivatives of human plasma (see *CLINICAL PHARMACOLOGY*,  
359 *Other Clinical Pharmacology Information (12.4) and WARNINGS/PRECAUTIONS, Infection Risk from Human Plasma (5.5)*).

360  
361 See *DOSAGE FORMS AND STRENGTHS (3)*.

**362 12 CLINICAL PHARMACOLOGY**

**363 12.1 Mechanism of Action**

364  
365 Upon mixing Sealer Protein (Human) and Thrombin (Human), soluble fibrinogen is transformed into fibrin, forming a rubber-like mass that adheres to the  
366 wound surface and achieves hemostasis and sealing or gluing of tissues.

**367 12.2 Pharmacodynamics**

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369 Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin (see *Pharmacokinetics (12.3)*).  
370 Fibrinolysis Inhibitor, Aprotinin (Synthetic), is a polyvalent protease inhibitor that prevents premature degradation of fibrin. Free Aprotinin and its  
371 metabolites have a half-life of 30 to 60 minutes and are eliminated by the kidney. Preclinical studies with different fibrin sealant preparations simulating  
372 the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of aprotinin in the  
373 product formulation increases resistance of the fibrin sealant clot to degradation in a fibrinolytic environment.

**374 12.3 Pharmacokinetics**

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

**378 12.4 Other Clinical Pharmacology Information**

**379 Viral Clearance**

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

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387 The virus reduction factors (expressed as log<sub>10</sub>) of manufacturing steps for each of the viruses tested are shown in Table 2.

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**Table 2.**

Reduction Factors for Virus Removal and/or Inactivation Sealer Protein Component					
Manufacturing Step	Mean Reduction Factors [log <sub>10</sub> ] 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 <sub>10</sub> ] 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

390 n.d. = not determined

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

394  
395 In addition, Human Parvovirus B19V was used to investigate the upstream Thrombin precursor mass capture step, the Sealer Protein early  
396 manufacturing steps and the Thrombin and Sealer Protein vapor heating steps. Using quantitative PCR assays, the estimated log reduction factors  
397 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 /  
398 Sealer Protein vapor heating steps, respectively.

**TISSEEL [Fibrin Sealant]**

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**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%)

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**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 resternotomy 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 $\chi^2$ two sided; $p < 0.0001$ ; intent-to-treat analysis	

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**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 ( $p = 0.067$ ,  $\chi^2$ , 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	$p < 0.001$

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**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

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**Storage**

**TISSEEL Kit (Freeze-Dried)**

Store at 2°C to 25°C. Avoid freezing.

**TISSEEL Pre-filled Syringe (Frozen)**

Long term: Store at  $\leq -20^\circ\text{C}$ .

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.

**TISSEEL [Fibrin Sealant]**

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455 **17 PATIENT COUNSELING INFORMATION**

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

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

460

461 **Baxter Healthcare Corporation**

462 Westlake Village, CA 91362 USA

463 US License No. 140

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465 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  
466 including patents pending.

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468 BAXTER, DUPLOJECT, FIBRINOTHERM and TISSEEL are trademarks of Baxter International Inc., registered in the U.S. Patent and Trademark Office.

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470 Revision Date: 01/2010