HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FIBRIN SEALANT (Human) safely and effectively. See full prescribing information for FIBRIN SEALANT (Human).

FIBRIN SEALANT (Human)
Frozen solutions of fibrinogen and thrombin
For Topical Use Only
Initial U.S. Approval: Month/YYYY

----------INDICATIONS AND USAGE----------

FIBRIN SEALANT (Human) is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. FIBRIN SEALANT (Human) is effective in heparinized patients. (1)

----------DOSAGE AND ADMINISTRATION----------

For Topical Use Only.

- After thawing, use FIBRIN SEALANT (Human) within 48 hours if stored at 2 ºC – 8 ºC [36 ºF - 46 ºF], or within 24 hours if stored at room temperature (20 °C – 25 °C [68 ºF - 77 ºF]), if it remains sealed in the original packaging. (2.2, 16)
- Prior to applying FIBRIN SEALANT (Human), use standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) to dry the surface area of the target bleeding site. (2.3)
- Apply FIBRIN SEALANT (Human) by dripping or spraying. When applying FIBRIN SEALANT (Human) using a spray device, ensure that the pressure and the distance from the tissue are within the recommended ranges. (2.3)
- Apply a sufficient volume of FIBRIN SEALANT (Human) to entirely cover the intended application area with a thin layer. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

FIBRIN SEALANT (Human) is supplied as a kit consisting of two separate packages:

- A package containing one syringe each of human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2) sterile frozen solutions which are assembled on a syringe holder.
- A package containing an application cannula.

FIBRIN SEALANT (Human) is available in the following package sizes:

Package size (Total volume)	Human fibrinogen	Human thrombin
2 mL	1 mL	1 mL
4 mL	2 mL	2 mL
6 mL	3 mL	3 mL
10 mL	5 mL	5 mL

----------CONTRAINDICATIONS----------

- Do not inject directly into the circulatory system. (4)
- Do not use for the treatment of severe or brisk arterial bleeding.
- Do not use in patients with history of anaphylaxis or severe systemic reactions to human blood products. (4)
- Do not use FIBRIN SEALANT (Human) for spraying unless the minimum recommended distance from the applicator tip to the bleeding site can be achieved. (2.3, 4)

----------WARNINGS AND PRECAUTIONS ----------

- Thromboembolic events may occur if FIBRIN SEALANT (Human) is administered intravascularly. (5.1)
- Life-threatening air or gas embolism may occur when using air- or gas-pressurized sprayers to administer fibrin sealants. Use the spray device at the recommended pressure and distance. When spraying FIBRIN SEALANT (Human), monitor blood pressure, pulse, oxygen saturation and end tidal CO_2. (5.2, 5.4)
- Do not spray in confined spaces. (5.2)
- Hypersensitivity reactions can occur. (5.3)
- May carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reactions (reported in >1% of clinical trial subjects) were nausea and procedural pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: MM/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 FIBRIN SEALANT (Human) is indicated as an adjunct to hemostasis for mild to moderate
4 bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques

(such as suture, ligature, and cautery) is ineffective or impractical. FIBRIN SEALANT (Human) is effective in heparinized patients.

2 DOSAGE AND ADMINISTRATION

For topical use only.

2.1 Dosage

Individualize application of the fibrin sealant. Individual doses typically ranged from 0.3 to 18.0 mL in the clinical studies. Larger volumes may be required for surgical procedures other than those included in the clinical studies.

The approximate surface area coverage for each FIBRIN SEALANT (Human) package size is provided in Table 1.

Table 1. Surface Area Coverage

FIBRIN SEALANT (Human) package size	**Surface area coverage (cm^2) Application by dripping or spray (1 mm thick layer)**
2 mL	14-20
4 mL	28-40
6 mL	42-60
10 mL	70-100

Dose depends on variables including, but not limited to, the type of surgical intervention, the size of the area, the intended application method, and the number of applications.

Apply a sufficient volume of FIBRIN SEALANT (Human) to entirely cover the intended application area with a thin layer. Repeat the application if necessary.

2.2 Preparation and Handling

Prepare and administer the product only according to the instructions and with the recommended devices.

Thawing

Room temperature

Thaw FIBRIN SEALANT (Human) at room temperature using the following steps:

1. Open the cardboard case and take out the inner contents.
2. Place the package with pre-filled syringes on a surface at room temperature (20 ºC - 25 ºC, [68 – 77 ºF])
   - for approximately 80 minutes for the 2 mL and the 4 mL package sizes
   - for approximately 120 minutes for the 6 mL and the 10 mL package sizes

After thawing, it is not necessary to warm the product for its use.

Water bath

Thaw FIBRIN SEALANT (Human) in a thermostatic water bath at a temperature not higher than 37 ºC [99 ºF] using the following steps:

1. Open the cardboard case and take out the inner contents.
2. Place the package with pre-filled syringes into water bath. At 37 ºC, the times needed are
   approximately 20 minutes for the 2 mL and the 4 mL package sizes
   approximately 30 minutes for the 6 mL and the 10 mL package sizes
3. Ensure the package remains submerged throughout thawing.

The temperature must not exceed 37 ºC.

Preparation

After thawing, FIBRIN SEALANT (Human) can be stored before use for not more than 48 hours in the refrigerator at 2-8 ºC [36 - 46 ºF] or 24 hours at room temperature (20 °C - 25 °C [68 - 77 ºF]) if it remains sealed in the original packaging.

After thawing, the solutions must be clear to slightly opalescent and colorless to pale yellow. Do not use solutions that are cloudy or have deposits.

Transferring instructions:

1. Remove the package from the surface at room temperature, from the refrigerator at 2 - 8 °C or from the water bath (and dry the outer pouch) after thawing.
2. Open the outer pouch and remove the sterile inner blister. See Figure 1.

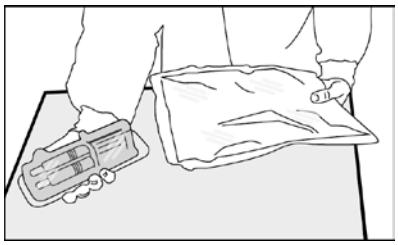

Figure 1

3. Open the inner blister and make the FIBRIN SEALANT (Human) syringe holder available to a second person for transfer to the sterile field. The outside of the blister package should not come in contact with the sterile field. See Figure 2.

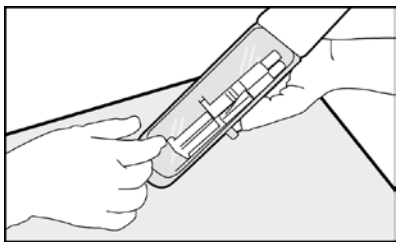

Figure 2

Connection instructions:

1. Hold the FIBRIN SEALANT (Human) syringe holder slightly inclined upwards.
2. Unscrew and remove the tip cap of both fibrinogen and thrombin syringes. See Figure 3.

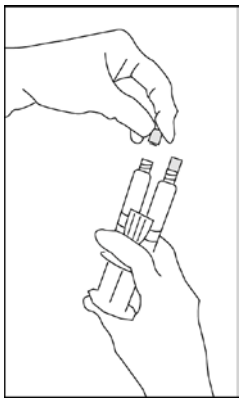

Figure 3

3. To remove air bubbles from syringes, strike gently the side of the syringes one or two times while keeping the syringe holder in an upright position and eject air. See Figure 4.

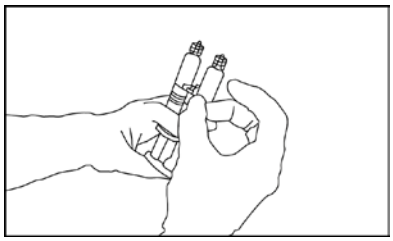

Figure 4

4. To attach the applicator tip, place it in the luer connector of the syringes and screw both syringe bodies counterclockwise consecutively, making a quarter (90 degree) turn each time. See Figure 5 for drip applicator. See Figure 6 for spray applicator.

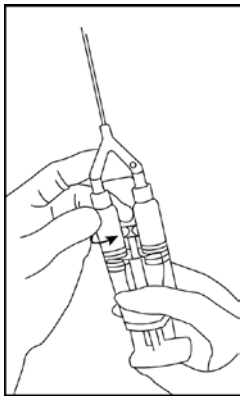

Figure 5

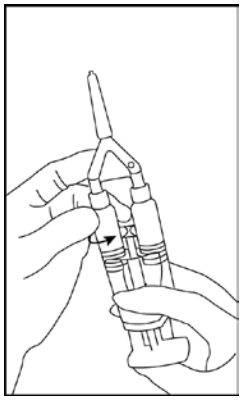

Figure 6

2.3 Administration

Apply FIBRIN SEALANT (Human) using the syringe holder and plunger link supplied.

Before administration of FIBRIN SEALANT (Human):

- To prevent tissue adhesion at undesired sites, protect (cover) parts of the body outside the intended application area. *[see Warnings and Precautions (5.4)]*
- Use standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) to dry the surface area of the target bleeding site.

Application by dripping

Apply FIBRIN SEALANT (Human) using the cannula provided with the product, or an equivalent cannula (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. When using the provided cannula, follow the connection instructions in the above section for Preparation. When using other applicator tips, follow the instructions for use of the tips.

Application by dripping instructions:

1. During dripping, keep the applicator tip as close as possible to the tissue surface without touching it.
2. Apply individual drops to the intended area.
3. To prevent uncontrolled clotting, allow the drops to separate from each other and from the applicator tip.

Application by spraying

Apply FIBRIN SEALANT (Human) using the Fibrijet Gas-assisted applicator spray device (not included in the kit), or an equivalent spray device (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. Always refer to the specific instructions provided with the device package.

When applying FIBRIN SEALANT (Human) using a spray device, ensure that the pressure is within the recommended range of 15 – 25 psi (1.0 – 1.7 bar). Do not exceed the pressure of 25 psi to avoid air or gas embolism. Do not spray closer than the recommended distance of 10 cm (3.9 inches) from the surface of the bleeding tissue.

Application by spraying instructions:

1. Connect the short gas tube on the application device to the luer-lock end of the filter tubing. See Figure 7.

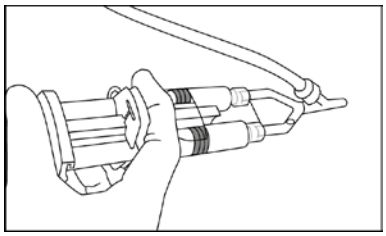

Figure 7

2. Connect the luer-lock of the gas tube to a pressure regulator capable of delivering 15 - 25 psi (1.0 – 1.7 bar) of gas pressure. See Figure 8.

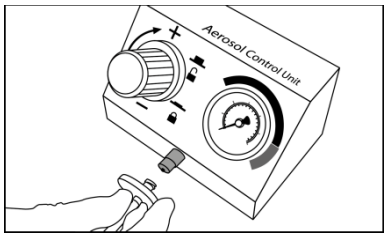

Figure 8

3. Spray the product onto the surface of the tissue in short bursts (0.1 – 0.2 ml) to form a thin, even layer.

Use the spray applicator with CO_2, nitrogen or medical air. To reduce the risk of potentially life-threatening air or gas embolism, spray FIBRIN SEALANT (Human) using pressurized CO_2. Use the pressure regulator according to the manufacturer's instructions *[see Warnings and Precautions (5.2)]*

3 DOSAGE FORMS AND STRENGTHS

FIBRIN SEALANT (Human) is supplied as a kit consisting of two separate packages:

- A package containing one syringe each of human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2) sterile frozen solutions which are assembled on a syringe holder.
- A package containing an application cannula.

The available package sizes of FIBRIN SEALANT (Human) are shown in Table 2.

Table 2. FIBRIN SEALANT (Human) Package Sizes

Package size (Total volume)	Human fibrinogen	Human thrombin
2 mL	1 mL	1 mL
4 mL	2 mL	2 mL
6 mL	3 mL	3 mL
10 mL	5 mL	5 mL

4 CONTRAINDICATIONS

- Do not inject directly into the circulatory system. *[see Warnings and Precautions (5.1)]*
- Do not use for the treatment of severe or brisk arterial bleeding. In these situations, blood flow will wash away FIBRIN SEALANT (Human) and prevent hemostasis.
- Do not use FIBRIN SEALANT (Human) in patients known to have anaphylactic or severe systemic hypersensitivity reactions to the administration of human blood products. *[see Warnings and Precautions (5.3)]*
- Do not use FIBRIN SEALANT (Human) for spraying unless the minimum recommended distance from the applicator tip to the bleeding site can be achieved. *[see Dosage and Administration (2.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis

Life-threatening thromboembolic complications may occur if FIBRIN SEALANT (Human) is administered intravascularly.

5.2 Gas or air embolism

Life-threatening air or gas embolism has occurred with spray devices employing pressure regulators to administer fibrin sealant products. This event appears to be related to using the spray device at higher than recommended pressures and in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2.

To minimize this risk, operate the spray device according to the instructions provided in section 2.3. *[see Dosage and Administration (2.3)]*

Monitor blood pressure, pulse, oxygen saturation, end tidal CO_2, and patient symptoms for evidence of air or gas embolism.

Do not spray in confined spaces.

5.3 Hypersensitivity

Allergic-type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, discontinue the administration of FIBRIN SEALANT (Human) immediately. Treat the reaction accordingly.

5.4 Application precautions

- Before administration of FIBRIN SEALANT (Human), protect (cover) parts of the body outside the desired application area to prevent tissue adhesion at undesired sites. *[see Dosage and Administration (2.3)]*
- Apply FIBRIN SEALANT (Human) as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process. *[see Dosage and Administration (2.1)]*
- Only spray FIBRIN SEALANT (Human) if it is possible to accurately judge the distance from the spray tip to the tissue surface. *[see Dosage and Administration (2.3)]*
- No clinical data are available to support the use of this product in neurosurgery or application through a flexible endoscope for treatment of bleeding.

5.5 Transmissible Infectious Agents

Because FIBRIN SEALANT (Human) is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. All suspected infections related to this product should be reported by the physician or other healthcare provider to Grifols Therapeutics Inc. at 1-800-520-2807. The physician should discuss the risks and benefits of the use of FIBRIN SEALANT (Human) with the patient. *[see Patient Counseling Information (17)]*

6 ADVERSE REACTIONS

The most common adverse reactions (reported in > 1% of clinical trial subjects) were nausea and procedural pain.

6.1 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 clinical practice.

Three clinical trials were conducted using the same general design, with each being randomized and active controlled. The types of surgeries included in each trial were different. Across all trials, 26% were vascular surgeries, 37% were parenchymous tissue surgeries, and 37% were soft tissue surgeries.

FIBRIN SEALANT (Human) was used to treat vascular bleeding during vascular surgery, or parenchymal bleeding during hepatic surgery, or soft tissue bleeding during retroperitoneal or pelvic surgery, abdominoplasties, or mastopexies, across all clinical trials, involving 500 trial subjects treated with FIBRIN SEALANT (Human), and 377 control subjects. The number of trial subjects treated with FIBRIN SEALANT (Human) for each type of surgery was 168 for vascular surgery, 163 for parenchymal surgery, and 169 for soft tissue surgery.

The FIBRIN SEALANT (Human) treatment group had a mean age of 57 years (standard deviation: 15.6 years; range: 0.3 to 86 years). The median age was 60 years. There were 11 subjects younger than 18 years old. There were 51% male subjects. 87% of the subjects exposed to FIBRIN SEALANT (Human) were White.

The mean volume of FIBRIN SEALANT (Human) used per subject and target bleeding site was 7 mL (standard deviation 3.5) and ranged from 0.3 to 18 mL. The median volume was 6 mL. Exposure to FIBRIN SEALANT (Human) consisted of a single intraoperative administration.

The clinical safety database included all subjects who received any amount of FIBRIN SEALANT (Human) in all clinical studies, with no exclusions.

In the FIBRIN SEALANT (Human) treatment group, 13% of trial subjects experienced one or more adverse reactions, and 8% of control subjects experienced one or more adverse reactions.

The adverse reactions shown in Tables 3-6 were evaluated as having a possible causal relationship to treatment with FIBRIN SEALANT (Human) and occurred in >1% of subjects.

Table 3. Adverse Reactions Occurring in >1% of Subjects in Vascular, Parenchyma, and Soft Tissue Surgery

MedDRA Preferred Term	N = 500 n (%);
Nausea	6 (1)
Procedural pain	10 (2)

Table 4. Adverse Reactions Occurring in >1% of Subjects in Vascular Surgery

MedDRA Preferred Term	N = 168 n (%)
Nausea	2 (1)
Pyrexia (fever)	2 (1)
Procedural pain	4 (2)
Vascular graft complication	2 (1)
Parvovirus B19 test positive	2 (1)
Urinary retention (Unable to empty the bladder completely)	2 (1)

Table 5. Adverse Reactions Occurring in >1% of Subjects in Parenchyma Surgery

MedDRA Preferred Term	N = 163 n (%)
Postprocedural bile leak	2 (1)
Procedural pain	2 (1)
Pulmonary embolism (Blood clot in the lungs)	2 (1)
Deep vein thrombosis (Blood clot that forms in a vein deep)	2 (1)

Table 6. Adverse Reactions Occurring in >1% of Subjects in Soft Tissue Surgery

MedDRA Preferred Term	N = 169 n (%)
Anemia (Low red blood cells)	2 (1)
Leukocytosis (Increased white blood cells)	2 (1)
Ileus (Decreased or absent movement of the stomach or intestine)	2 (1)
Nausea	4 (2)
Procedural pain	4 (2)
Alanine aminotransferase increased	2 (1)
Aspartate aminotransferase increased	2 (1)
Hypocalcaemia (Low serum calcium)	2 (1)
Hypokalaemia (Low serum potassium)	2 (1)
Hyponatraemia (Low serum sodium)	2 (1)
Prothrombin time prolonged (Increased bleeding time)	2 (1)
Headache	2 (1)
Insomnia	2 (1)
Pruritus (Itching)	4 (2)
Hypertension	2 (1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with FIBRIN SEALANT (Human) use in pregnant women. Animal reproduction studies have not been performed with FIBRIN SEALANT (Human). It is unknown whether FIBRIN SEALANT (Human) can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. In the U.S. general population, the estimated background risk of major birth defect and miscarriage is clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of FIBRIN SEALANT (Human) in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FIBRIN SEALANT (Human) and any potential adverse effects on the breastfed infant from FIBRIN SEALANT (Human) or from the underlying maternal condition.

8.4 Pediatric Use

Only limited clinical data are available regarding the use of FIBRIN SEALANT (Human) in children. A total of 11 out of 500 subjects administered FIBRIN SEALANT (Human) in the clinical trials were pediatric subjects. Of these 11 subjects, 5 were infants aged less than 2 years, 5 were children between the ages of 2 and 11 years, and 1 was an adolescent aged between 12 and 16 years. Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials included 172 subjects aged 65 years or older treated with FIBRIN SEALANT (Human). No differences in safety or effectiveness were observed between these subjects and younger subjects.

11 DESCRIPTION

FIBRIN SEALANT (Human) is a two-component fibrin sealant consisting of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) sterile solutions filled in syringes which are assembled on a syringe holder.

FIBRIN SEALANT (Human) is supplied as frozen solutions. After thawing, the human fibrinogen and human thrombin solutions are clear or slightly opalescent and colorless or pale yellow. FIBRIN SEALANT (Human) does not contain any preservatives.

Fibrinogen

Component 1 is a sterile solution, pH 6.5 – 8.0, which contains concentrated human fibrinogen and excipients. Fibrinogen is a protein from human blood that forms a clot when combined with thrombin. The composition of the human fibrinogen solution is as follows:
Active ingredient: human fibrinogen (80 mg/mL)
Other ingredients: sodium citrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium and water for injection.

Thrombin

Component 2 is a sterile solution, pH 6.0 – 8.0, which contains purified human thrombin and excipients. Thrombin is a specific protease that activates clotting of the final combined product and converts fibrinogen to fibrin. The composition of the human thrombin solution is as follows:
Active ingredient: human thrombin (500 IU/mL)
Other ingredients: calcium chloride, human albumin, sodium chloride, glycine and water for injection.

The starting material for the production of both fibrinogen and thrombin components of FIBRIN SEALANT (Human) is pooled human Source Plasma obtained from FDA-licensed plasma collection centers in the United States. Cohn's plasma fractionation method is used to obtain Fraction I, which is the starting material for the production of fibrinogen, and the prothrombin complex isolated from supernatant of Fraction I, which is the starting material for the production of thrombin. The purification process of fibrinogen includes solvent/detergent treatment, three glycine precipitation steps, and double nanofiltration using 35-nm and 20-nm filters. The purification process of thrombin includes solvent/detergent treatment, ion exchange chromatography, and double nanofiltration through 15-nm filters. After nanofiltration, the

fibrinogen and thrombin solutions are formulated, sterile filtered, aseptically filled in syringes, packaged, sterilized, and frozen.

Viral safety

Individual plasma donations used in the manufacture of FIBRIN SEALANT (Human) are collected in FDA-licensed plasma donation centers in the U.S. and are tested for viral markers in compliance with the U.S. regulatory requirements. In addition, mini-pools of plasma units are tested as an in-process control for hepatitis A virus (HAV) and parvovirus B19 (B19V) using validated nucleic acid testing (NAT) methods. All the tests must be non-reactive (negative) except for B19V, for which the limit in plasma manufacturing pools does not exceed a titer of 10^4 IU/mL. The manufacturing plasma pool is also tested with NAT for HBV, HCV, and HIV, and all the tests must be non-reactive (negative).

The manufacturing processes for fibrinogen and thrombin include processing steps which are designed to reduce the risk of viral transmission. Both components have two discrete steps with viral clearance capacity, namely solvent/detergent treatment (with 1.0% (v/v) Tween 80/0.30% (v/v) tri-n-butyl phosphate (TNBP) for 6.0 – 6.5 hours at 27.0 ± 1.5 ºC for fibrinogen or 25 ± 1 ºC for thrombin), validated to inactivate enveloped viruses, and a nanofiltration step validated to remove non-enveloped and enveloped viruses (35-nm and 20-nm filters for fibrinogen and two 15-nm filters for thrombin). Additionally, the glycine precipitation steps contribute to the overall safety of the product in the purification process of human fibrinogen. The Fraction I precipitation and ion-exchange chromatography steps contribute to the overall safety of the product in the purification process of human thrombin.

The viral clearance capacity of these virus inactivation/removal procedures has been validated in small-scale *in vitro* studies using relevant and model viruses with a range of physico-chemical characteristics. The results of viral clearance validation studies are summarized in Tables 7 and 8:

Table 7. Global Virus Reduction Factors (Log_{10}) for Human Fibrinogen

Manufacturing step	**Virus reduction factor (log_{10})***					
	Enveloped viruses				Non-enveloped viruses	
	HIV-1	PRV	WNV	BVDV	HAV	PPV
S/D treatment	≥ 5.33	≥ 6.80	≥ 5.20	≥ 5.60	n.a.	n.a.
Glycine precipitations	n.d.	n.d.	n.d.	n.d.	5.21	2.09
Nanofiltration 35 nm and 20 nm	≥ 5.57	≥ 6.09	≥ 4.51	≥ 4.53	5.22	4.37
Global virus reduction factor (log_{10})	≥ 10.90	≥ 12.89	≥ 9.71	≥ 10.13	10.43	6.46

Table 8. Global Virus Reduction Factors (Log_{10}) for Human Thrombin

Manufacturing step	Virus reduction factor (log_{10})*					
	Enveloped viruses				Non-enveloped viruses	
	HIV-1	PRV	WNV	BVDV	HAV	PPV
Fraction I precipitation	< 1.0	2.13	2.78	1.34	1.18	< 1.0
S/D treatment	≥ 5.52	≥ 5.85	≥ 5.94	≥ 5.09	n.a.	n.a.
SP-Sepharose XL chromatography	n.d.	n.d.	n.d.	n.d.	4.61	3.97
Double nanofiltration 15 nm	≥ 4.03	≥ 5.95	≥ 5.42	≥ 4.93	6.56	6.14
Global virus reduction factor (log_{10})	≥ 9.55	≥ 13.93	≥ 14.14	≥ 11.36	12.35	10.11

*: Reduction factor below 1 log_{10} is not considered in calculating the global virus reduction; n.d.: Not done; n.a.: Not applicable; BVDV: bovine viral diarrhea virus, model for HCV; WNV: West Nile virus; PRV: pseudorabies virus, model for large enveloped DNA viruses; PPV: porcine parvovirus, model for B19V

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FIBRIN SEALANT (Human) contains human fibrinogen and human thrombin. When applied onto the wound site and mixed, these biological components generate a cross-linked fibrin clot in a process that recreates the last stage of the human blood coagulation system. Fibrinogen is converted into fibrin monomers and fibrinopeptides by thrombin. The fibrin monomers aggregate and form a fibrin clot which stops the bleeding. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both the conversion of fibrinogen and the crosslinking of fibrin.

12.2 Pharmacodynamics

There are no relevant pharmacodynamic data on FIBRIN SEALANT (Human).

12.3 Pharmacokinetics

FIBRIN SEALANT (Human) is metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis. No pharmacokinetic studies were conducted for Fibrin Sealant (Human).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of FIBRIN SEALANT (Human) or its effects on fertility.

14 CLINICAL STUDIES

Vascular surgery

A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of FIBRIN SEALANT (Human) as adjunct to hemostasis in vascular surgery. Subjects

underwent vascular surgical procedures utilizing polytetrafluoroethylene graft material on proximal end-to-side arterial anastomosis or upper extremity vascular access arterial anastomosis. FIBRIN SEALANT (Human) was shown to be superior to the control group (manual compression) when comparing the proportion of subjects in each group who achieved hemostasis by 4 minutes (Table 9). Superiority was also established at 10 minutes. The median time to hemostasis was significantly shorter (p-value <0.001) in the FIBRIN SEALANT (Human) treatment group (4.0 minutes) compared to the control group (≥10.0 minutes).

Table 9. Efficacy Results in Vascular Surgery (ITT Population)*

Efficacy endpoints	**FIBRIN SEALANT (Human) N=109 n (%)**	**Control N=57 n (%)**	**Ratio of -proportions[1] (95% CI)**	**P-value**
Hemostasis by 4 minutes	83 (76.1)	13 (22.8)	3.3 (2.0, 5.4)	<0.001
Hemostasis by 10 minutes	96 (88.1)	26 (45.6)	1.9 (1.4, 2.6)	<0.001

*Intent-to-treat (ITT) population: includes all subjects randomized to FIBRIN SEALANT (Human) or control.
[1]The ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups (FIBRIN SEALANT (Human) ® relative to control).
CI = confidence interval.
Tabulated efficacy results are cumulative results.

Parenchyma surgery

A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of FIBRIN SEALANT (Human) as adjunct to hemostasis in parenchyma surgery. Subjects underwent liver resections. FIBRIN SEALANT (Human) was shown to be superior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes (Table 10).

The median time to hemostasis was significantly shorter (p-value <0.001) in the FIBRIN SEALANT (Human) treatment group (2.0 minutes) compared to the control group (3.0 minutes).

Table 10. Efficacy Results in Liver Surgery (ITT Population)*

Efficacy endpoints	**FIBRIN SEALANT (Human) N = 111 n (%)**	**Control N = 113 n (%)**	**Ratio of proportions [1] (95% CI)**	**P-value**
Hemostasis by 4 minutes	103 (92.8)	91 (80.5)	1.2 (1.0, 1.3)	0.010
Hemostasis by 2 minutes	62 (55.9)	47 (41.6)	1.3 (1.0, 1.8)	0.045

*Intent-to-treat (ITT) population: includes all subjects randomized to FIBRIN SEALANT (Human) or control.
[1]The ratio of proportions of subjects meeting the efficacy endpoint in the two treatment groups (FIBRIN SEALANT (Human) relative to control).
CI = confidence interval
Tabulated efficacy results are cumulative results.

Soft tissue surgery

A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of FIBRIN SEALANT (Human) as adjunct to hemostasis in soft tissue bleeding during

retroperitoneal and pelvic surgical procedures, and during mastopexies and abdominoplasties. FIBRIN SEALANT (Human) was shown to be non-inferior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes (Table 11).

Table 11. Efficacy results in retroperitoneal and pelvic surgery, mastopexies and abdominoplasties (ITT population)*

Efficacy endpoints	FIBRIN SEALANT (Human) N = 116 n (%)	Control N = 108 n (%)	Ratio of proportions [1] (95% CI)	P-value
Hemostasis by 4 minutes	96 (82.8)	84 (77.8)	1.1 (0.9, 1.2)	0.401

*Intent-to-treat (ITT) population: includes all subjects randomized to FIBRIN SEALANT (Human) or control.
[1]The ratio of proportions of subjects meeting the efficacy endpoint in the two treatment groups (FIBRIN SEALANT (Human) relative to control).CI = confidence interval.
Tabulated efficacy results are cumulative results.

16 HOW SUPPLIED/STORAGE AND HANDLING

FIBRIN SEALANT (Human) is supplied as a single-use kit comprised of two pre-filled syringes containing sterile frozen solutions of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2), which are assembled on a single syringe holder. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biological components. One application cannula is co-packaged with the product for application by dripping. FIBRIN SEALANT (Human) may also be applied with a spray application device such as Fibrijet Gas-assisted applicator spray device or an equivalent spray device cleared by FDA for this use.

The available package sizes for FIBRIN SEALANT (Human) are shown in Table 12.

Table 12. FIBRIN SEALANT (Human) Package Sizes and NDC numbers

FIBRIN SEALANT (Human) Package Size			NDC Numbers	
Total Volume	Human fibrinogen	Human thrombin	Carton	Blister label
2 mL	1 mL	1 mL	61953-0011-1	61953-0011-2
4 mL	2 mL	2 mL	61953-0012-3	61953-0012-4
6 mL	3 mL	3 mL	61953-0013-5	61953-0013-6
10 mL	5 mL	5 mL	61953-0014-7	61953-0014-8

Store the kit with the frozen package of FIBRIN SEALANT (Human) in a freezer (at -18 °C [0 ºF] or colder) for up to 2 years. The cold storage condition must not be interrupted until use. Thaw before use. Once thawed, do not refreeze.

After thawing, FIBRIN SEALANT (Human) can be stored before use for not more than 48 hours at 2 – 8 ºC [36 - 46 ºF] or 24 hours at room temperature (20 - 25 °C [68 - 77 ºF]) if it remains sealed in the original packaging. Once the package is opened, use FIBRIN SEALANT (Human) immediately during the surgery and discard any unused contents.

Keep the pouch containing the sterile blister in the outer carton to protect from light.

Do not use after the expiration date printed on the outer carton and container labels. Discard if the package is damaged.

17 PATIENT COUNSELING INFORMATION

Instruct patients to immediately report to their physician symptoms of thrombosis or embolism which may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body *[see Thrombosis (5.1)]*.

Inform patients that FIBRIN SEALANT (Human) is made from human plasma and may carry a risk of transmitting infectious agents (e.g., viruses, the vCJD agent and, theoretically, the CJD agent). Instruct patients to report any symptoms that concern them and might be caused by infections.

Manufactured by:
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