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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VISTASEAL™ safely and effectively. See full prescribing information for VISTASEAL.

VISTASEAL™ [Fibrin Sealant (Human)]
Frozen solutions of fibrinogen and thrombin
For Topical Use Only
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	9/2024
Dosage and Administration (2)	9/2024

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

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

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

For topical use only.

- The recommended dose of VISTASEAL is based on the surface area coverage as described in Section 2.1 Table 1.
- After thawing, use VISTASEAL within 7 days if stored at 2 °C - 8 °C [36 °F - 46 °F], or within 24 hours if stored at room temperature (20 °C - 25 °C [68 °F - 77 °F]), if it remains sealed in the original packaging. (2.2, 16)
- Prior to applying VISTASEAL, 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 VISTASEAL by dripping or spraying. When applying VISTASEAL using a spray device, ensure that the distance from the tissue is within the recommended ranges for the applicator tip used. (2.3, 2.4)
- Apply a sufficient volume of VISTASEAL to entirely cover the intended application area with a thin layer. (2.1, 2.4)

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

VISTASEAL 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 in a syringe holder. (3)
- A package containing a VISTASEAL Dual Applicator with two additional Airless Spray Tips. (3)

VISTASEAL 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. (4)
- Do not use in patients with history of anaphylaxis or severe systemic reactions to human blood products. (4)
- Do not use VISTASEAL for spraying unless the minimum recommended distance from the applicator tip to the bleeding site can be achieved. (4)

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

- Thromboembolic events may occur if VISTASEAL is administered intravascularly. (5.1)
- Hypersensitivity reactions can occur. (5.2)
- 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. (5.3)

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

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

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VISTASEAL, a fibrin sealant (human), is indicated as an adjunct to hemostasis for mild to moderate bleeding in patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VISTASEAL is effective in heparinized patients.

2 DOSAGE AND ADMINISTRATION

For topical use only.

2.1 Dosage

The recommended dose of VISTASEAL is based on the surface area coverage.

The approximate surface area coverage for each VISTASEAL package size is provided in Table 1.

Table 1. Surface Area Coverage

VISTASEAL package size	Surface area coverage (cm^2) Application by dripping or spray (1 mm thick layer)
2 mL	16 - 22
4 mL	32 - 44
6 mL	48 - 66
10 mL	80 - 110

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 VISTASEAL 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.

An overview of thawing methods and storage after thawing is provided in Table 2.

Table 2. Thawing and storage after thawing

Thawing method	Thawing time per package size		Maximum storage time after thawing
	For 2 mL and 4 mL	For 6 mL and 10 mL	
Refrigerator (2 – 8 °C [36 – 46 °F])	Minimum 7 hours	Minimum 10 hours	7 days at 2 - 8 °C [36 – 46 °F] (refrigerator) in original package OR 24 hours at 20 - 25 °C [68 - 77 °F] (room temperature) in original package

Thawing method	Thawing time per package size		Maximum storage time after thawing
	For 2 mL and 4 mL	For 6 mL and 10 mL	
Room Temperature (20 - 25 °C [68 – 77 °F])	Minimum 70 minutes	Minimum 90 minutes	7 days at 2 - 8 °C [36 – 46 °F] (refrigerator) in original package OR 24 hours at 20 - 25 °C [68 - 77 °F] (room temperature) in original package
Sterile water bath set at 37 °C [99 °F] inside sterile field. The water temperature must not exceed 39 °C [102 °F].	Minimum 5 minutes. Do not exceed 10 minutes.	Minimum 5 minutes. Do not exceed 10 minutes.	Use immediately during the surgery

Preferred thawing methods

Option 1: Refrigerator thawing

1. Remove carton from freezer and place it unopened in the refrigerator for thawing at 2 – 8 °C [36 – 46 °F] for
   a minimum of 7 hours for the 2 mL and the 4 mL package sizes
   a minimum of 10 hours for the 6 mL and the 10 mL package sizes

After thawing, it is not necessary to warm the product for its use.
After thawing, the solutions must be clear to slightly opalescent, colorless to pale yellow and must not be cloudy nor have deposits.

Option 2: Room Temperature thawing

Remove carton from freezer, open it and take out the two blisters.
Place the blister containing the VISTASEAL Dual Applicator at room temperature until the VISTASEAL fibrin sealant (human) is ready to use.

Thaw blister with VISTASEAL pre-filled syringes at room temperature using the following steps:

1. Place the blister containing the syringe holder with pre-filled syringes on a surface at room temperature (20 °C - 25 °C, [68 - 77 °F]) for
   a minimum of 70 minutes for the 2 mL and the 4 mL package sizes
   a minimum of 90 minutes for the 6 mL and the 10 mL package sizes

After thawing, it is not necessary to warm the product for its use.
After thawing, the solutions must be clear to slightly opalescent, colorless to pale yellow and must not be cloudy nor have deposits.

Post-Thawing Storage:

After thawing, the kit containing the VISTASEAL syringe holder with pre-filled syringes and Dual Applicator can be stored before use for not more than 7 days in the refrigerator at 2 - 8 °C

[36 - 46 °F] or 24 hours at room temperature (20 - 25 °C [68 - 77 °F]) if it remains sealed in the original packaging. Once the blisters are opened, use VISTASEAL immediately during the surgery and discard any unused contents.
Once thawed, do not refreeze.

Transferring instructions:

1. After thawing, remove the blister from the surface at room temperature or remove carton from the refrigerator at 2 - 8 °C [36 - 46 °F] and take out the two blisters.
2. Open the blister and confirm that the VISTASEAL pre-filled syringes are completely thawed. After thawing, the solutions must be clear to slightly opalescent, colorless to pale yellow and must not be cloudy nor have deposits. Make the VISTASEAL syringe holder with pre-filled syringes available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field. See Figure 1.

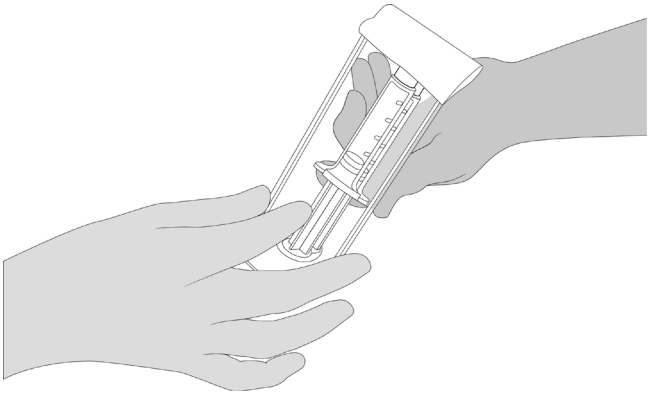

Figure 1

<u>Sterile Water Bath (Quick Thawing) method</u>
Remove carton from freezer, open it and take out the two blisters.
Place the blister containing the VISTASEAL Dual Applicator at room temperature until the VISTASEAL fibrin sealant (human) is ready to use.

Thaw VISTASEAL pre-filled syringes inside the sterile field in a sterile thermostatic water bath set at a temperature of 37 °C [99 °F] using the following steps:
NOTE: Prepare and maintain the sterile water bath following the instructions of the water bath manufacturer and according to hospital procedures to maintain a sterile surgical field and avoid the possibility of contamination.
NOTE: Once the VISTASEAL blisters are opened, use the product immediately during surgery. Use sterile technique to avoid the possibility of contamination due to improper handling, and follow the steps below accurately. Do not remove the syringe luer cap until thawing is complete and the Dual Applicator is ready to be attached.

1. Open the blister and make the VISTASEAL syringe holder with pre-filled syringes available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field. See Figure 1.
2. Place the syringe holder with pre-filled syringes directly into the sterile water bath ensuring that it is completely immersed in the water. See Figure 2.
3. At 37 °C, the time needed is approximately 5 minutes for the 2 mL, 4 mL, 6 mL, and 10 mL package sizes, but must not be left at this temperature for longer than 10 minutes.
   NOTE: The temperature of the water must not exceed 39°C. To monitor the water temperature, you may use a thermometer and change the water as necessary.

4. Dry the syringe holder with pre-filled syringes after thawing, using a sterile surgical gauze.

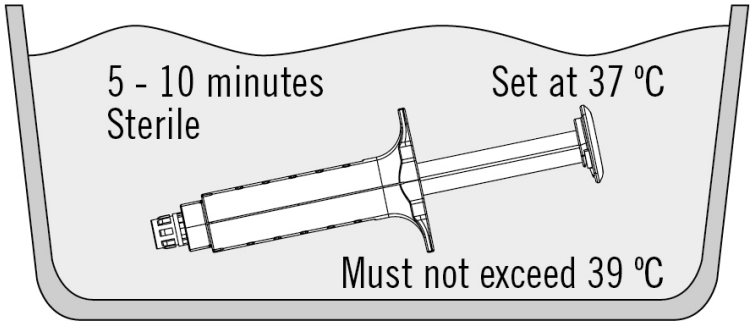

Figure 2

Confirm that the VISTASEAL pre-filled syringes are completely thawed. After thawing, the solutions must be clear to slightly opalescent, colorless to pale yellow and must not be cloudy nor have deposits.
Use VISTASEAL immediately during the surgery and discard any unused contents.

Connection instructions

1. Open the blister and make the VISTASEAL Dual Applicator and two additional Airless Spray Tips available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field.
2. Hold the VISTASEAL syringe holder with syringe luer caps pointed upward. See Figure 3.
3. Unscrew and discard the syringe luer cap of both fibrinogen and thrombin syringes. See Figure 3.

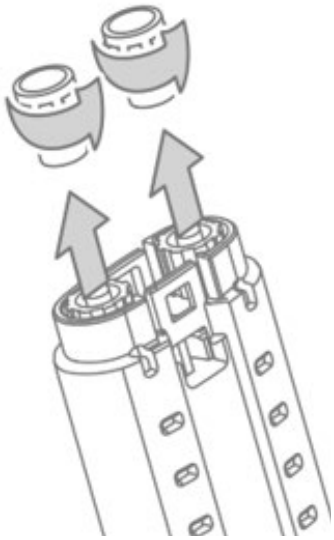
Figure 3

4. Hold the syringe holder with the luers pointed upward. To remove air bubbles from syringes, strike gently the side of the syringe holder one or two times while keeping the syringe holder in an upright position and lightly depress the plunger to eject air. See Figure 4.

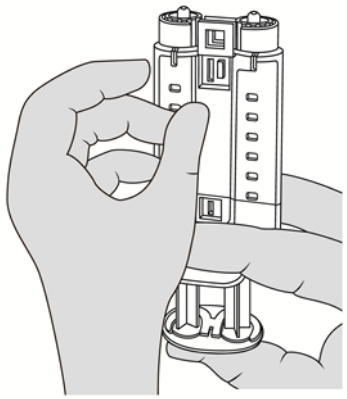

Figure 4

5. Attach the Dual Applicator. See Figure 5.
NOTE: Do not depress plunger during attachment or prior to intended use because the two biologic components will pre-mix in the Airless Spray Tip, forming a fibrin clot that prevents dispensing. See Figure 6.

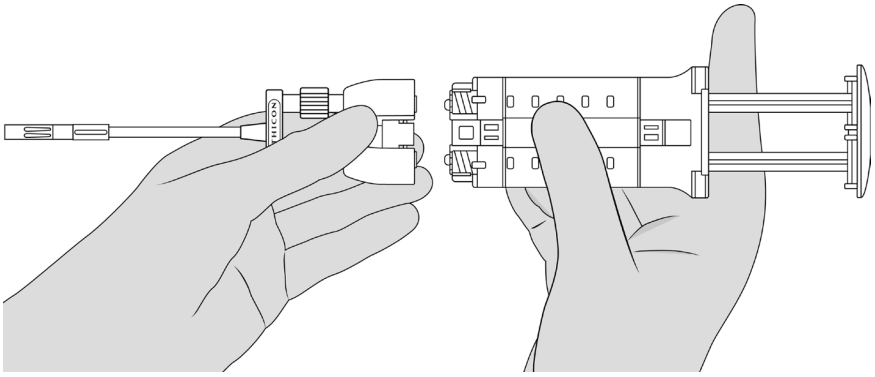

Figure 5

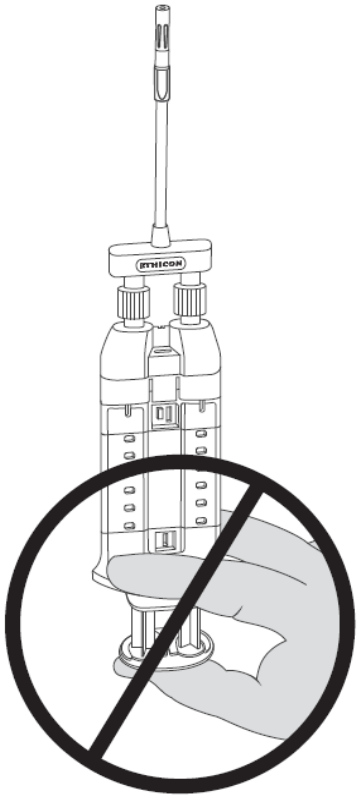

Figure 6

6. Tighten luer locks and ensure the Dual Applicator is firmly attached. The device is now ready to use.

2.3 Administration

For topical use only.

Apply VISTASEAL using the syringe holder and plunger supplied.

Apply VISTASEAL using the Dual Applicator provided with the product. Applicator tips cleared by the FDA for specific use with the VISTASEAL may also be used. When using the provided Dual Applicator, follow the connection instructions in the above section for Preparation. When using other applicator tips, follow the instructions for use that are provided with the applicator tips.

Before administration of VISTASEAL

- To prevent tissue adhesion at undesired sites, protect (cover) parts of the body outside the intended application area. *[see Dosage and Administration (2.4)]*
- Use standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) to dry the surface area of the target bleeding site.

<u>Application by spraying</u>

1. Grasp and bend the Dual Applicator to the desired position. Tip will retain its shape.

2. Position the Airless Spray Tip at least 2 cm away from the target tissue. Apply firm even pressure to the plunger to spray the fibrin sealant. Increase distance accordingly to achieve desired coverage of the target area.
3. If expression is stopped for any reason, change the Airless Spray Tip prior to resuming application since a clot may form inside the Airless Spray Tip. To change the Airless Spray Tip, remove the device from the patient and unscrew the used Airless Spray Tip. See Figure 7. Place the used Airless Spray Tip away from the spare Airless Spray Tips. Wipe the end of the applicator using dry or moist sterile surgical gauze. Then, connect a new Airless Spray Tip provided in the package and ensure it is firmly connected before use.
   NOTE: Red indicator will not be visible if Airless Spray Tip is properly connected. See Figure 8.
   NOTE: Do not continue pushing the plunger in an attempt to clear the fibrin clot within the Airless Spray Tip; otherwise the applicator may become unusable.
   NOTE: Do not trim the Dual Applicator to avoid exposing internal wire.

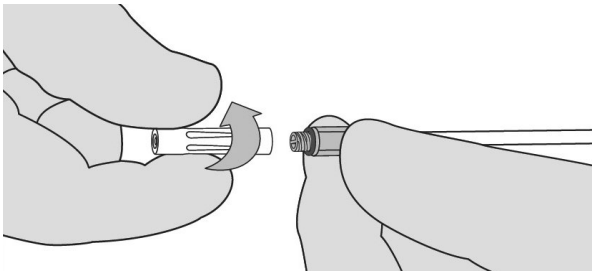

Figure 7

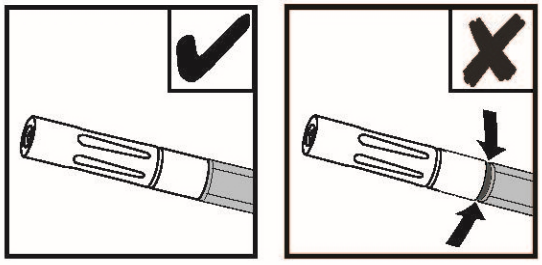

Figure 8

Application by dripping

1. Remove the Airless Spray Tip portion of the spray and drip tip by unscrewing the Airless Spray Tip.
   See Figure 7.
2. Grasp and bend the drip tip to the desired position. Tip will retain its shape.
3. During dripping, keep the end of the drip tip as close to the tissue surface as possible without touching the tissue during application.
4. Apply individual drops to the surface area to be treated. To prevent uncontrolled clotting, allow the drops to separate from each other and from the end of the drip tip.
   NOTE: Do not reconnect a used drip tip after it has been removed from the adapter; otherwise a clot may form inside the drip tip and the applicator may become unusable.

2.4 Application precautions

- Before administration of VISTASEAL, 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 VISTASEAL 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 VISTASEAL 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.

3 DOSAGE FORMS AND STRENGTHS

VISTASEAL 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 a Dual Applicator with two additional Airless Spray Tips.

The available package sizes of VISTASEAL are shown in Table 3.

Table 3. VISTASEAL 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 VISTASEAL and prevent hemostasis.
- Do not use VISTASEAL in patients known to have anaphylactic or severe systemic hypersensitivity reactions to the administration of human blood products. *[see Warnings and Precautions (5.2)]*
- Do not use VISTASEAL 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 VISTASEAL is administered intravascularly.

5.2 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 VISTASEAL immediately. Treat the reaction accordingly.

5.3 Transmissible Infectious Agents

Because VISTASEAL 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 LLC at 1-800-520-2807. The physician should discuss the risks and benefits of the use of VISTASEAL with the patient. *[see Patient Counseling Information (17)]*

6 ADVERSE REACTIONS

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.

The safety data described in this section reflect exposure to VISTASEAL in four clinical studies. A total of 591 patients (489 adults and 102 pediatric) received VISTASEAL for vascular (Study 1), parenchymal (Study 2 and Study 4), or soft tissue (Study 3 and Study 4) surgery. *[see Clinical Studies (14)]*

The most frequently occurring adverse reactions are shown in Tables below.

In the VISTASEAL group in these 4 trials, 11% of trial patients experienced one or more adverse reactions, and 7% of control patients experienced one or more adverse reactions.

Table 4. Adverse Reactions Occurring in >1% of Patients in Study 1, 2, and 3 and Study 4 (Combined)

Preferred Term	N = 591 n (%)
Procedural pain	11 (2)
Nausea	6 (1)

Table 5. Adverse Reactions Occurring in >1% of Patients in Study 1

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

Table 6. Adverse Reactions Occurring in >1% of Patients in Study 2

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 7. Adverse Reactions Occurring in >1% of Patients in Study 3

Preferred Term	N = 169 n (%)
Nausea	4 (2)
Procedural pain	4 (2)
Pruritus (Itching)	4 (2)
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)
Alanine aminotransferase increased	2 (1)
Aspartate aminotransferase increased	2 (1)
Hypocalcemia (Low serum calcium)	2 (1)
Hypokalemia (Low serum potassium)	2 (1)
Hyponatremia (Low serum sodium)	2 (1)
Prothrombin time prolonged (Increased bleeding time)	2 (1)
Headache	2 (1)
Insomnia	2 (1)
Hypertension	2 (1)

Additionally, in the pediatric clinical study (Study 4) conducted to assess safety and efficacy of VISTASEAL compared to EVICEL (human fibrin sealant), one adverse reaction (procedural pain) occurred in one patient (1%) who received VISTASEAL. *[see Pediatric Use (8.4) and Clinical Studies [14]]*

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of VISTASEAL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General disorders and administration site conditions: adhesions

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with VISTASEAL use in pregnant women. Animal reproduction studies have not been performed with VISTASEAL. It is unknown whether VISTASEAL 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 in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of VISTASEAL 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 VISTASEAL and any potential adverse effects on the breastfed infant from VISTASEAL or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of VISTASEAL have been established in pediatric patients as an adjunct to hemostasis during surgery. The use of VISTASEAL for this indication is supported by evidence from adequate and well-controlled studies for assessment of safety and efficacy in pediatric patients in the following age groups: 4 neonates (aged ≤ 27 days), 24 infants (aged ≥ 28 days to 23 months), 39 children (aged 2 years to < 12 years) and 39 adolescents aged 12 years to < 18 years of age. *[see Adverse Reactions (6.1) and Clinical Studies (14)]*

8.5 Geriatric Use

Clinical trials included 172 patients aged 65 years or older treated with VISTASEAL. No differences in safety or effectiveness were observed between these patients and younger patients.

11 DESCRIPTION

VISTASEAL 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 in a syringe holder.

VISTASEAL is supplied as frozen solutions. After thawing, the human fibrinogen and human thrombin solutions are clear or slightly opalescent and colorless or pale yellow. VISTASEAL 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 VISTASEAL 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 VISTASEAL 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 °C for fibrinogen or 25 ± 1 °C 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 8 and 9:

Table 8. 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 9. 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

VISTASEAL 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 VISTASEAL.

12.3 Pharmacokinetics

VISTASEAL is metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis. No pharmacokinetic studies were conducted for VISTASEAL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of VISTASEAL or its effects on fertility.

14 CLINICAL STUDIES

The effectiveness of VISTASEAL was demonstrated in four clinical studies in patients undergoing vascular (Study 1), parenchymal (Study 2 and Study 4), or soft tissue (Study 3 and Study 4) surgery. The details of the studies are described below.

Study 1 (Vascular surgery)
A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of VISTASEAL as adjunct to hemostasis in vascular surgery. Patients underwent vascular surgical procedures utilizing polytetrafluoroethylene graft material on proximal end-to-side arterial anastomosis or upper extremity vascular access arterial anastomosis. The clinical trial was conducted with VISTASEAL using a Fibrijet® applicator.

The primary efficacy outcome was to demonstrate superiority of VISTASEAL compared to manual compression (control) in achieving hemostasis by 4 minutes.

The study enrolled 166 patients with a median age of 64.0 years for VISTASEAL and 61.0 years for control (overall range across groups 22 to 84 years). The population characteristics included 65% Male, 90.4% White, 8.4% Black or African American, 1.2% Asian, 3.0% Hispanic or Latino patients.

VISTASEAL was shown to be superior to the control group (manual compression) when comparing the proportion of patients in each group who achieved hemostasis by 4 minutes (Table 10). Superiority was also established at 10 minutes. The median time to hemostasis was significantly shorter (p-value <0.001) in the VISTASEAL group (4.0 minutes) compared to the control group (≥10.0 minutes).

The efficacy results are summarized in Table-10 below.

Table 10. Efficacy Results in Study 1 (ITT Population)*

Efficacy endpoints	VISTASEAL 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 patients randomized to VISTASEAL or control.
[1]The ratio of proportion of patients meeting the efficacy endpoint in the two treatment groups (VISTASEAL relative to control).
CI = confidence interval.
Tabulated efficacy results are cumulative results.

Study 2 (Parenchyma surgery)
A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of VISTASEAL as adjunct to hemostasis in parenchyma surgery. Patients underwent liver resections. The clinical trial was conducted with VISTASEAL using a Fibrijet® applicator. The primary efficacy outcome was to demonstrate superiority of VISTASEAL compared to oxidized regenerated cellulose (control) in achieving hemostasis by 4 minutes.

The study enrolled 224 patients with a median age of 61.0 years in each arm (overall range across groups 19 to 84 years). The population characteristics included 54.5% male, 93.3% White, 1.3% Black or African American, 4.5% Asian, 0.4% American Indian or Alaskan Native, 0.4% not specified, 5.4% Hispanic or Latino.

VISTASEAL was shown to be superior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes (Table 11). The median time to hemostasis was significantly shorter (p-value <0.001) in the VISTASEAL group (2.0 minutes) compared to the control group (3.0 minutes).

Table 11. Efficacy Results in Study 2 (ITT Population)*

Efficacy endpoints	**VISTASEAL 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 patients randomized to VISTASEAL or control.
[1]The ratio of proportions of patients meeting the efficacy endpoint in the two treatment groups (VISTASEAL relative to control).
CI = confidence interval
Tabulated efficacy results are cumulative results.

Study 3 (Soft tissue surgery)
A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of VISTASEAL as adjunct to hemostasis in soft tissue bleeding during retroperitoneal and pelvic surgical procedures, and during mastopexies and abdominoplasties. The clinical trial was conducted with VISTASEAL using a Fibrijet® applicator.

The primary efficacy outcome was to demonstrate non-inferiority of VISTASEAL compared to oxidized regenerated cellulose (control) in achieving hemostasis by 4 minutes.

The study enrolled 224 patients with the median age of 46.0 years for VISTASEAL and 45.0 years for control (overall range across groups 15 to 85 years). The population characteristics included 22.8% male, 77.7% White, 21% Black or African American, 0.9% Asian, 0.4% American Indian or Alaskan Native, 14.3% Hispanic or Latino patients.

The efficacy outcomes are summarized in Table 12 below.

Table 12. Efficacy results in Study 3 (ITT population)*

Efficacy endpoints	VISTASEAL 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 patients randomized to VISTASEAL.
[1]The ratio of proportions of patients meeting the efficacy endpoint in the two treatment groups (VISTASEAL relative to control).
CI = confidence interval.
Tabulated efficacy results are cumulative results.

Study 4 (Pediatric parenchyma surgery and soft tissue surgery)

A prospective, multicenter, randomized, active controlled, single-blind, clinical trial conducted to evaluate the safety and efficacy of VISTASEAL as an adjunct to hemostasis during open parenchyma (hepatic) surgery or soft tissue surgery. The clinical trial was conducted with fibrin sealant (human) using a Fibrijet® applicator and VistaSeal™ Dual Applicator with airless tips.

The primary efficacy outcome was to demonstrate non-inferiority of VISTASEAL compared to EVICEL in achieving hemostasis by 4 minutes.

A total of 178 pediatric patients (6 neonates, 37 infants, 63 children, and 72 adolescents) were randomized and treated with VISTASEAL(n=91) or EVICEL as active control (n=87). Of the 178 patients, 89 underwent parenchyma (hepatic) surgical procedures and 89 had soft tissue surgeries. The population characteristics included 63% male, 94% White, 4% Black or African American, <1% Asian, <1% multiple races, and <1% other race patients.

Exposure to VISTASEAL consisted of a single intraoperative administration. The mean volume of VISTASEAL used per pediatric patient was 4.6 mL ± 2.7 mL.

The efficacy outcomes are summarized in Table 13 below.

Table 13. Efficacy results in Study 4 (mITT population)*

Efficacy endpoints	VISTASEAL N = 91 n (%)	Control N = 87 n (%)	Ratio of proportions [1] (95% CI)	P-value
Hemostasis by 4 minutes	88 (96.7)	83 (95.4)	1.01 (0.96, 1.07)	<0.001

*Modified intent-to-treat (ITT) population: includes all patients randomized who met intraoperative criteria and were treated with any amount of study product.
[1]The ratio of proportions of patients meeting the efficacy endpoint in the two treatment groups (VISTASEAL relative to control). If the lower limit of the 95% CI was above the non-inferiority margin 0.8, it could be claimed that VISTASEAL was not inferior to EVICEL.
CI = confidence interval.
Tabulated efficacy results are cumulative results.

Additional information from the pediatric surgery study is described in Adverse Reactions and Use in Specific Populations Pediatric Use *[see Adverse Reactions (6.1) and Pediatric Use (8.4)]*

16 HOW SUPPLIED/STORAGE AND HANDLING

VISTASEAL kit is comprised of two separate packages (blisters). One package includes 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 syringe holder for single use. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biological components. One Dual Applicator with two additional Airless Spray Tips, in the other package, is co-packaged with the product for application by spraying or dripping. The Airless Spray Tips are radiopaque. See Figure 9.

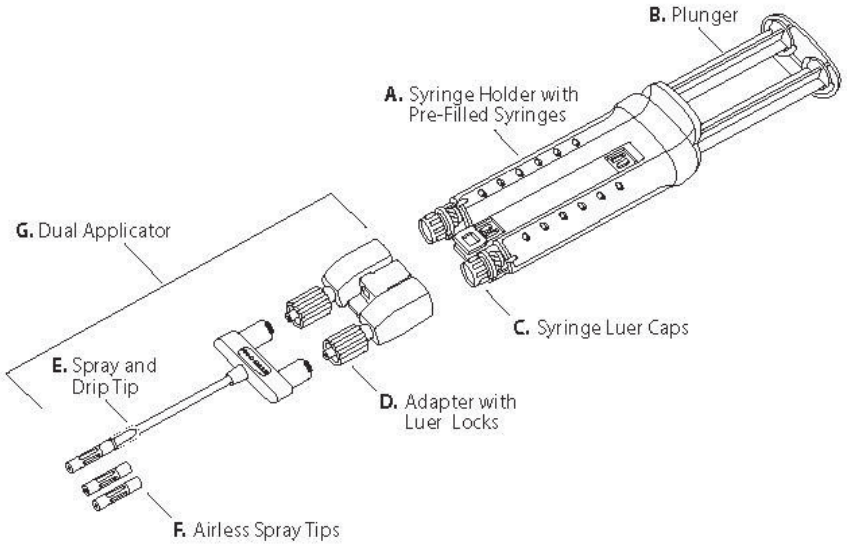

Figure 9

The available package sizes for VISTASEAL and their color codes are shown in Table 14.

Table 14. VISTASEAL Package Sizes and NDC numbers

VISTASEAL Package Size			NDC Numbers		Color Code
Total Volume	**Human fibrinogen**	**Human thrombin**	**Carton**	**Blister label**	
2 mL	1 mL	1 mL	61953-0020-1	61953-0020-2	Green box
4 mL	2 mL	2 mL	61953-0020-3	61953-0020-4	Orange box
6 mL	3 mL	3 mL	61953-0020-5	61953-0020-6	Blue box
10 mL	5 mL	5 mL	61953-0020-7	61953-0020-8	Purple box

Storage

Store the frozen kit (VISTASEAL fibrin sealant (human) with VISTASEAL Dual Applicator) in a freezer (at -18 °C [0 °F] 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, VISTASEAL can be stored before use for not more than 7 days at 2 - 8 °C [36 - 46 °F] or 24 hours at room temperature (20 - 25 °C [68 - 77 °F]) if it remains sealed in the original packaging (blister). Once the blister is opened, use VISTASEAL immediately during the surgery and discard any unused contents.

Keep the sterilized 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

Discuss the following with patient receiving VISTASEAL.

- Thrombosis: 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)]*

- Hypersensitivity: Inform patient that hypersensitivity reaction may occur with VISTASEAL. Advise patient to seek immediate medical evaluation if any signs and symptoms of hypersensitivity occur such as itching, rash or hives, or breathing problems. *[see Warnings and Precautions (5.2)]*

- Transmissible Infectious Agents: Inform patients that VISTASEAL 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. *[see Warnings and Precautions (5.3)]*

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