Baxter

FLOSEAL Hemostatic Matrix, 5 mL/10 mL

Instructions for Use

Caution: Federal Law (United States) restricts this device to sale by or on the order of a licensed healthcare practitioner.

DO NOT INJECT INTRAVASCULARLY.

FLOSEAL Hemostatic Matrix, also referred to as FLOSEAL Matrix, must not be injected into blood vessels.

Device Description:

The FLOSEAL Matrix kit consists of a bovine-derived Gelatin Matrix component, a human-derived Thrombin component, Applicator tips, and mixing accessories. The mixing accessories include a syringe for Matrix preparation, containing 0.9% Sodium Chloride Solution and a vial adapter for needle-free reconstitution. The accessories are included to facilitate the reconstitution and mixing of the Thrombin into the Gelatin Matrix. Applicator tips are included to facilitate the delivery of FLOSEAL Matrix to the site to be treated. (For specific package contents, see Table in "How Supplied" section.)

The Gelatin Matrix consists of cross-linked gelatin granules and is provided sterile and non-pyrogenic in a disposable syringe. The Thrombin (Human) is a sterile, non-pyrogenic, freeze-dried, vapor-heated and solvent/detergent treated powder preparation made from pooled human plasma. The Sodium Chloride Solution is a sterile, non-pyrogenic solution. After reconstitution of the lyophilized Thrombin with Sodium Chloride Solution, the resulting Thrombin solution contains 500 units*/mL Thrombin (Human).

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

Thrombin (Human) is prepared from pooled human plasma through a series of separation and filtration steps followed by incubation of the solution with Calcium Chloride in order to activate prothrombin to Thrombin. The Thrombin (Human) solution subsequently undergoes ultra/diafiltration, vapor heat treatment, solvent/detergent treatment, sterile filtration and freeze-drying.

Thrombin (Human) is made from pooled human plasma obtained from U.S. licensed plasma collection centers. The two-step vapor-heated and solvent/detergent treatment used in its manufacture has been shown to be capable of significant viral reduction. However, no procedure has been shown to be completely effective in removing viral infectivity from derivatives of human plasma (see "Warnings").

The manufacturing procedure for FLOSEAL Matrix includes processing steps designed to reduce the risk of viral transmission. Several steps are included in the manufacture of the Gelatin Matrix component that reduce the risk of viral transmission. The virus reduction factors (expressed as $\log_{10}$) for the manufacture of the Gelatin Matrix component are provided in the table below.

Reduction Factors for Virus Removal and/or Inactivation During the Manufacture of Gelatin Matrix

Manufacturing Step	Virus Reduction Factor of Virus Tested	
	BVDV	PPV
Base Treatment (NaOH)	>5.4	4.0
Chemical Cross-linking	>5.0	1.1
Heat Treatment	>6.5	1.9

BVDV: Bovine viral diarrhea virus, a model for Hepatitis C virus; **PPV** Porcine parvovirus, a model for non-enveloped viruses, among those, Hepatitis A virus.

A two-step vapor-heated and solvent/detergent viral inactivation treatment process is included in the manufacture of Thrombin. The virus reduction factors (expressed as $\log_{10}$) for Thrombin are provided in the table below.

Reduction Factors for Virus Removal and/or Inactivation Thrombin Component

Manufacturing Step	Mean Reduction Factors [$\log_{10}$] of Virus Tested					
	HIV-1	HAV	BVDV	PRV	MMV	B19V
Thrombin precursor mass capture	3.2	1.5	1.8	2.5	1.2	1.7
Vapor Heat Treatment	>5.5	>4.9	>5.3	>6.7	1.0	>4
Solvent/Detergent Treatment	>5.3	n.d.	>5.5	>6.4	n.d.	n.d.
Ion Exchange Chromatography	n.d.	n.d.	n.d.	n.d.	3.6	n.d.
Overall Reduction Factor (ORF)	>14.0	>6.4	>12.6	>15.6	5.8	>5.7

n. d. = not determined

HIV-1: Human immunodeficiency virus 1; **HAV**: Hepatitis A virus; **BVDV**: Bovine viral diarrhea virus, a model for Hepatitis C virus; **PRV**: Pseudorabies virus, a model for enveloped DNA viruses, among those Hepatitis B virus; **MMV**: Mice minute virus, a model for Human Parvovirus B19; **B19V**: Human Parvovirus B19.

FLOSEAL Matrix is the combination of the Gelatin Matrix component and the reconstituted Thrombin (Human) component. Thrombin must be added to the Gelatin Matrix component prior to use. FLOSEAL Matrix is biocompatible and resorbed within 6 to 8 weeks, consistent with normal wound healing. FLOSEAL Matrix is intended only for topical administration.

Indications:

FLOSEAL Matrix is indicated in surgical procedures (other than in ophthalmic) as an adjunct to hemostasis when control of bleeding, by ligature or conventional procedures is ineffective or impractical.

Contraindications:

- Do not inject or compress FLOSEAL Matrix into blood vessels. Do not apply FLOSEAL Matrix in the absence of active blood flow, e.g., while the vessel is clamped or bypassed, as extensive intravascular clotting and even death may result.
- To avoid a risk of allergic-anaphylactoid reaction and/or thromboembolic events, which may be life-threatening, do not inject FLOSEAL Matrix into a vessel or tissue.
- Do not use FLOSEAL Matrix in patients with known allergies to materials of bovine origin.
- Do not use FLOSEAL Matrix in the closure of skin incisions because it may interfere with the healing of the skin edges due to mechanical interposition of gelatin.

Warnings:

- FLOSEAL Matrix contains Thrombin made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses. Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation. The physician should discuss the risks and benefits of this product with the patient.
- FLOSEAL Matrix is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis. FLOSEAL Matrix is not intended to be used as a prophylactic hemostatic agent.
- Excess FLOSEAL Matrix (material not incorporated in the hemostatic clot) should always be removed by gentle irrigation and suctioned out of the wound. Meticulous irrigation is required when used in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, the brain and/or cranial nerves.
- FLOSEAL Matrix swells by approximately 10-20% after product is applied and surgeons should consider its potential effect on the surrounding anatomic areas. Maximum swell volume is achieved within about 10 minutes.
- FLOSEAL Matrix should not be used in the presence of infection. FLOSEAL Matrix should be used with caution in contaminated areas of the body. If signs of infection or abscess develop where FLOSEAL Matrix has been applied, re-operation may be necessary in order to remove the infected material and allow drainage.
- The safety and effectiveness of FLOSEAL Matrix for use in ophthalmic procedures has not been established.
- FLOSEAL Matrix should not be used for controlling post-partum bleeding or menorrhagia.
- The safety and effectiveness of FLOSEAL Matrix has not been established in children under 2 years of age and pregnant women.
- Do not use air to remove residual FLOSEAL Matrix from Applicator tip.

Precautions:

General

- For single use only. Do not re-sterilize.
- As with other hemostatic agents, do not apply FLOSEAL Matrix to sites where there is negative peripheral venous pressure (e.g. due to patient positioning), as material may be drawn into the vascular system potentially resulting in life-threatening thromboembolic events.
- Since the Thrombin solution can be denatured by contact with solutions containing alcohol, iodine, or heavy metal ions, FLOSEAL Matrix should not be applied before the application site is cleaned to remove any antiseptics that may contain such substances.
- When placed into cavities or closed tissue spaces, gentle approximation is advised (Do not compress.).
- As with other hemostatic agents, do not aspirate FLOSEAL Matrix into extracorporeal cardiopulmonary bypass circuits or autologous blood salvage circuits. It has been demonstrated that fragments of collagen based hemostatic agents may pass through 40µm transfusion filters of blood scavenging systems.
- Do not use FLOSEAL Matrix on bone surfaces where adhesives, such as methylmethacrylate or other acrylic adhesives, will be required to attach a prosthetic device. Microfibrillar collagen has been reported to reduce the strength of methylmethacrylate adhesives used to attach prosthetic devices to bone surfaces.
- FLOSEAL Matrix should not be used for the primary treatment of coagulation disorders.
- The safety and effectiveness of the combined use of FLOSEAL Matrix with antibiotic solutions or powders has not been established.
- The safety and effectiveness for use in neurosurgical and urological procedures has not been established through randomized clinical studies.
- In urological procedures, FLOSEAL Matrix should not be left in the renal pelvis or ureters to eliminate the potential foci for calculus formation.
- Do not cut Applicator tips, as tissue injury from sharp edges may result.

Information for Patients

- Some viruses, such as human parvovirus B19, are particularly difficult to remove or inactivate at this time. Human parvovirus B19 most seriously affects pregnant women, or immune-compromised individuals. Symptoms of human parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash, and joint pain. Patients should be encouraged to consult their physician if such symptoms appear.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Use in Pregnancy

- It is not known whether FLOSEAL Matrix can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLOSEAL Matrix should be administered to a pregnant woman only if clearly needed.

FLOSEAL Matrix Adverse Events:

In a randomized prospective, concurrently controlled clinical trial using a formulation of FLOSEAL Matrix containing bovine Thrombin, a total of 309 patients received FLOSEAL Matrix or the Control (Gelatin Sponge + Thrombin). The most common adverse events recorded during and after the application of the hemostatic agents were anemia, atrial fibrillation, infection, and hemorrhage. The following is a complete list of adverse events reported in greater than 1% of patients that were observed in the pivotal clinical trial for the FLOSEAL Matrix group. The corresponding adverse events for the Control group are listed for comparison. None of the adverse events that occurred were judged by the surgeon to be "Probably Related" to the use of FLOSEAL Matrix.

Adverse Events Reported in Greater than 1% of Patients in the FLOSEAL Matrix Clinical Trial

Adverse Event	FLOSEAL Matrix	Control (Gelatin Sponge + Thrombin)
Anemia	12 (8%)	7 (4%)
Fibrillation Atrial	10 (6%)	8 (5%)
Infection	10 (6%)	11(7%)
Hemorrhage	6 (4%)	6 (4%)
Pneumonia	6 (4%)	2 (1%)
Urinary Tract Infection	6 (4%)	3 (2%)
Rash	5 (3%)	3 (2%)
Edema	5 (3%)	1 (<1%)
Hypotension	4 (3%)	2 (1%)
Respiratory Distress	4 (3%)	3 (2%)
Confusion	4 (3%)	0 (0%)
Dural Tear	4 (3%)	4 (3%)
Fibrillation Ventricular	4 (3%)	3 (2%)
Arrhythmia	4 (3%)	0 (0%)
Heart Failure Right	3 (2%)	2 (1%)
Thrombosis Arterial	3 (2%)	8 (5%)
Fever	3 (2%)	2 (1%)
Atelectasis	3 (2%)	1 (<1%)
Pleural Effusion	3 (2%)	5 (3%)

Counts reflect number of patients in each treatment group reporting one or more adverse events that map to a Modified COSTART 5th edition body system. At each level of summarization (Adverse Event), patients are only counted once.

Other adverse events observed in 1% or less of the FLOSEAL Matrix clinical trial patients were myocardial infarction, cellulitis, pneumothorax, pain, cerebrovascular accident, hallucination, paresthesia, bradycardia, abscess, diarrhea, urinary retention, dehiscence, skin ulcer, transfusion reaction, dyspnea, heart arrest, lung edema, back pain, ventricular tachycardia, neuropathy, acute kidney failure, kidney tubule necrosis, gastritis, nausea, nausea and vomiting, skin rash, hyperglycemia, and heel ulcer.

The following adverse events, all rated "mild", were deemed by the surgeon to be "Possibly Related" to the use of FLOSEAL Matrix: anemia (2 patients, 1%), mild post-operative bleeding (1 patient, <1%), and local inflammation (1 patient, <1%). No other adverse events were deemed by the surgeon to be related to the use of FLOSEAL Matrix.

Allergic reactions may be encountered in people who are sensitive to bovine materials.

Only the amount of Floseal necessary to achieve hemostasis should be used. Excess Floseal (material not incorporated in the hemostatic clot) should always be removed by gentle irrigation from the site of application. Any Floseal not removed at the time of surgery may result in diagnostic imaging confusion, e.g. present itself as a (recurring) mass or a (space occupying) lesion, or may lead to a foreign body reaction with or without clinical signs and symptoms.

Erectile dysfunction has been reported when Floseal was used in surgical procedures involving the cavernous nerves occasionally exposed in radical prostatectomy procedures.

Gelatin-Based Hemostatic Agents Adverse Events:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- Excess gelatin-based hemostatic agents should always be removed by gentle irrigation from the site of application. Removal of excess is done to avoid excessive inflammatory reaction, adhesion and/or granuloma formation.
- Giant cell granulomas have been observed at implant sites when used in the brain.
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid has been observed.
- Multiple neurologic events were reported when absorbable gelatin-based hemostatic agents were used in laminectomy operations, including cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence.
- The use of absorbable gelatin-based hemostatic agents during the repair of dural defects associated with laminectomy and craniotomy operations has been associated with fever, infection, leg paresthesias, neck and back pain, bladder and bowel incontinence, cauda equina syndrome, neurogenic bladder, impotence, and paresis.
- The use of absorbable gelatin-based hemostatic agents has been associated with paralysis, due to device migration into foramina in the bone around the spinal cord, and blindness, due to device migration in the orbit of the eye, during lobectomy, laminectomy and repair of a frontal skull fracture and lacerated lobe.
- Foreign body reactions, "encapsulation" of fluid, and hematoma have been observed at implant sites.
- Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin-based sponges were used in severed tendon repair.
- Toxic shock syndrome was reported in association with the use of absorbable gelatin-based hemostats in nasal surgery.
- Fever, failure of absorption, and hearing loss have been observed when absorbable hemostatic agents were used during tympanoplasty.

Human Thrombin Adverse Events:

As with any other plasma derivates, anaphylactoid or anaphylactic reactions may occur in rare cases. No adverse events of this type were reported during the course of clinical trials using a different product containing the same human Thrombin component. Mild reactions can be managed with antihistamines; severe hypotensive reactions require immediate intervention using current principles of shock therapy.

Equivalence of Bovine and Human Thrombin:

The performance of FLOSEAL Matrix containing human Thrombin was compared to that of original FLOSEAL Matrix (containing bovine Thrombin) in a bleeding liver square model in pigs.

Blood flow rates for the lesions created in the pig liver model were recorded at specific time points and statistically analyzed by the method of Blackwelder and Chang modified for continuous variables. This analysis demonstrates that the performance of FLOSEAL Matrix (human Thrombin) is equivalent to the performance of FLOSEAL Matrix (bovine Thrombin) with a p-value of < 0.001 at each of the time intervals.

In addition, each lesion was subjectively scored for bleeding at each time point. These data points were analyzed using the method of Blackwelder and Chang for proportions.

The results for all lesions in all animals showed FLOSEAL Matrix (human Thrombin) and FLOSEAL Matrix (bovine Thrombin) were equivalent for each of the time intervals with a p-value of 0.015.

Clinical Studies:

Study Design and Objectives: A prospective, randomized, controlled, multi-center, multi-specialty study was conducted using a formulation of FLOSEAL Matrix containing bovine Thrombin. Three hundred and nine (309) patients were enrolled at 10 centers. The objective of the study was to evaluate the safety and effectiveness of FLOSEAL Matrix, compared to a commercially available control hemostat, Absorbable Gelatin Sponge, USP ("Gelatin Sponge") + Thrombin, in controlling intraoperative bleeding. This study was designed to show that the FLOSEAL Matrix success rate was equivalent to the success rate for the Control.

Patients undergoing surgery in cardiac, vascular or spinal/orthopedic surgical specialties were included.

Patients were randomized only after it was determined that the bleeding could not be controlled using conventional approaches (e.g. direct pressure, sutures and/or cautery) because of their ineffectiveness or impracticality. Success at achieving hemostasis was defined as cessation of bleeding within 10 minutes following application of the agent. The primary endpoint was hemostasis success for the first treated bleeding site. A secondary endpoint was time to hemostasis for the first treated bleeding site. Although multiple bleeding sites in the same patient were treated, only the first treated bleeding site was used to determine primary effectiveness, as this was the only site that was truly randomized.

Clinical Study Results:

Primary Endpoint: The primary endpoint, cessation of bleeding within 10 minutes of the first lesion, achieved a success rate of 96% in the FLOSEAL Matrix group and 77% in the Control group. FLOSEAL Matrix and Control were shown to be equivalent using the Blackwelder and Chang test, using a Δ (clinically significant difference) of 0.15 ($p<0.0001$). The difference between FLOSEAL Matrix and Control was also shown to be statistically significant using the Cochran-Mantel-Haenszel test ($p<0.001$). Primary endpoint data were stratified for individual surgical specialties, and the results are summarized in the table below:

Hemostasis Within 10 Minutes – First Lesion Only (Intent-to-Treat Patients)

Patient Category	FLOSEAL Matrix	Control
All Patients	96% (149/156)	77% (118/153)
Cardiac	94% (45/48)	60% (27/45)
Vascular	93% (40/43)	76% (35/46)
Spinal/Orthopedic	98% (64/65)	90% (56/62)

In the cardiac cohort, 88 of the 93 patients (95%) underwent surgery with extracorporeal cardiopulmonary bypass. FLOSEAL Matrix was used for hemostasis prior to heparin reversal by the administration of protamine sulfate in 19 of 46 patients. Protamine sulfate reverses the anticoagulative effects of heparin. Results for hemostasis at 10 minutes for the heparinized patients in both the FLOSEAL Matrix and Control groups, before and after protamine sulfate reversal of heparin, are shown in the table below:

Hemostasis Success at 10 Minutes Before and After Protamine Administration (Cardiac Patients Only)

Group	Before Protamine	After Protamine
FLOSEAL Matrix	89% (17/19)	96% (26/27)
Control	36% (5/14)	75% (21/28)

The success rate for FLOSEAL Matrix did not appear to be affected by whether or not the patient had received protamine sulfate administration. This was demonstrated by the fact that the success rate for FLOSEAL Matrix before protamine sulfate administration was similar to the success rate after protamine sulfate administration whereas the Control hemostat success rate was clearly lower before protamine sulfate reversal of heparin was administered.

Secondary Endpoint: A secondary endpoint was time to hemostasis for the first treated bleeding site. The data for time to hemostasis are summarized in the table below.

Cumulative Percent of Patients with Complete Hemostasis First Lesion (Protocol Valid Patients*)

Time Interval	FLOSEAL Matrix	Control
0 – 1 minute	41% (62/153)	21% (32/150)
1 – 2 minutes	69% (106/153)	32% (48/150)
2 – 3 minutes	85% (130/153)	48% (72/150)
3 – 6 minutes	93% (143/153)	68%(102/150)
6 – 10 minutes	97% (149/153)	77% (115/150)

**Six (6) patients, 3 in the FLOSEAL Matrix group and 3 in the Control group, were excluded because of protocol deviations in measuring hemostasis for the first treated bleeding site.*

When the data were stratified by surgical specialty, the median times to hemostasis were shorter for the FLOSEAL Matrix group than for the Control group in all specialties. The median times are summarized in the table below.

Time to Hemostasis First Lesion Only (Protocol Valid Lesions)

Median Time to Hemostasis in minutes (95% Confidence Interval*)

Patient Category	FLOSEAL Matrix	Control
All Patients	2.0 (1.5, 2.5)	6.0 (5.5, 6.0)
Cardiac	2.8 (2.0, 4.0)	8.0 (6.0, 8.5)
Vascular	2.5 (2.0, 4.0)	6.5 (4.5, 8.0)
Spinal/Orthopedic	1.5 (1.0, 1.5)	3.0 (2.0, 4.5)

**Confidence interval using a Bonferroni correction.*

Use of FLOSEAL Matrix as a Hemostatic Agent for Nasal/ Sinus Bleeding:

FLOSEAL Matrix has been used as a hemostatic agent for the control of operative and post-operative bleeding (epistaxis) during nasal/sinus surgery in 18 patients (30 application sites). Patients were followed for 24 hours following surgery and all complications and episodes of epistaxis were recorded during this period. Intraoperative bleeding stopped in 30 of 30 (100%) application sites. No intraoperative complications were reported in this group. One patient presented with epistaxis 6 hours postoperatively; this patient was treated uneventfully and released from the hospital on the first postoperative day.

Use of FLOSEAL Matrix as a Hemostatic Agent in Cardiovascular Surgery

FLOSEAL Matrix was tested in a prospective randomized controlled trial[1] in 209 patients and compared to 206 control patients treated with either oxidized regenerated cellulose SURGICEL hemostat, or purified porcine skin gelatin GELFOAM® hemostat. Patients underwent elective cardiac and/or thoracic aortic operations.

Study endpoints included rate of successful intraoperative hemostasis, time required for hemostasis (defined as operative time comprised between decannulation and closure of the sternum), overall postoperative bleeding, rate of transfusion of blood products, rate of surgical revision for bleeding, postoperative morbidity and intensive care unit stay. Patients were followed-up for 96 hours postoperatively.

In the cohort of patients having intraoperative bleeding treated with FLOSEAL Matrix (n=110), a decreased hemostasis time was observed (32.1 ± 5.4 minutes vs. 56.3 ± 8 minutes, p <0.001) as compared to control n=104). Furthermore a decrease in transfusion of blood products (28.2% vs. 60.6%, p <0.001), revision rate (4.5% vs. 13.5%, p=0.04) and minor complications (20.9% vs. 33.6%, p = 0.04) was observed in the FLOSEAL Matrix group as compared to control. Minor complications were defined as either renal failure, respiratory insufficiency or inotropic support lasting more than 24 hours.

No difference in major complications (stroke, shock, sepsis or myocardial infarction) or ICU stay was observed between groups.

Reference

1. Nasso G, Piancone F, Bonifazi R, et al. Prospective, randomized clinical trial of the FloSeal matrix sealant in cardiac surgery. Ann Thorac Surg 2009;88(5):1520-1526.

How Supplied:

FLOSEAL Matrix is provided in the configuration shown in the table below.

FLOSEAL Hemostatic Matrix Kit Configuration		
REF	Gelatin Matrix Pouch	Thrombin Component Pouch
ADS201844 5 mL Kit	• 1 x 5 mL syringe with Gelatin Matrix • 1 x 5 mL syringe for Matrix Preparation, containing 0.9% Sodium Chloride Solution • 1 x standard applicator tip • 1 x malleable applicator tip	• 1 x vial Thrombin (Human), Vapor Heated, Solvent /Detergent treated, 2500 IU • 1 x Needle-free vial adaptor
ADS201845 10 mL Kit	• 1 x 10 mL syringe with Gelatin Matrix • 1 x 10 mL syringe for Matrix Preparation, containing 0.9% Sodium Chloride Solution • 1 x standard applicator tip • 1 x malleable applicator tip	• 1 x vial Thrombin (Human), Vapor Heated, Solvent /Detergent treated, 5000 IU • 1 x Needle-free vial adaptor

Directions for Use:

Thrombin must be added to the Gelatin Matrix prior to use.

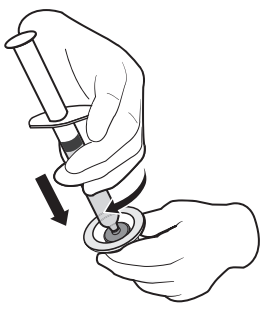
Inspect the integrity of the contents of the FLOSEAL kit. If the packaging, syringe(s) or vial have been damaged or opened, do not use.

Opening the package

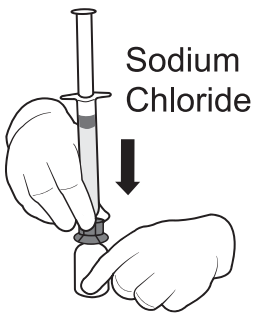
- Using aseptic technique, open the outer pouch containing the Thrombin components and deliver the sterile inner pouch to the sterile field. Items in this pouch will be used to reconstitute the Thrombin prior to mixing with the Gelatin Matrix. Once placed in the sterile field, the inner pouch may be opened at any time.
- Repeat the above procedure with the pouch containing the Gelatin Matrix Components and deliver the sterile inner package to the sterile field. Once placed in the sterile field, the inner package may be opened at any time.
- Do not connect the Gelatin Syringe with 0.9% Sodium Chloride Solution prior to reconstituting Thrombin.

Preparing the Thrombin solution

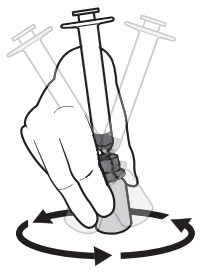
- Remove the lid from the vial adapter packaging.
- Remove the cap from the Syringe for Matrix preparation, containing 0.9% Sodium Chloride Solution and discard the cap.
- While gripping the vial adapter packaging, attach the syringe to the Luer connector of the vial adapter and remove it from remaining packaging.



- Remove the plastic flip-off cap from the Thrombin vial. While holding the vial adapter / syringe assembly, pierce the rubber stopper of the Thrombin vial.

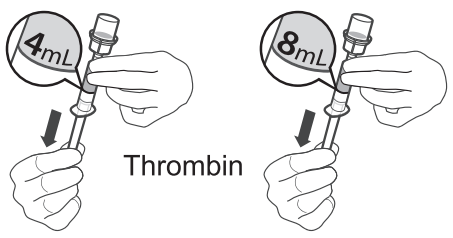


- Transfer the entire contents of the syringe into the Thrombin vial. If needed, the syringe plunger may be pushed to expel the remaining contents of the vial.
- Loosen the syringe connection one quarter (1/4) turn to release the vacuum in the vial, then re-tighten syringe.
- Facilitate reconstitution of the Thrombin by holding the vial and gently swirling it with the syringe and vial adapter attached until the Thrombin is completely dissolved.



- Once reconstituted, the Thrombin Solution can be used to prepare FLOSEAL Matrix immediately or may be stored in the vial up to four (4) hours.
- Aspirate the Thrombin Solution to the fill line on the syringe.

NOTE: Draw up 4 mL Thrombin solution for FLOSEAL Matrix 5 mL kit; draw up 8 mL for FLOSEAL Matrix 10 mL kit.



- When ready to prepare the FLOSEAL Matrix, disconnect the syringe from the vial adapter and proceed to mix with the Gelatin Matrix granules following the steps in the next section.
- Discard the remaining Thrombin solution, Thrombin vial and vial adapter appropriately.

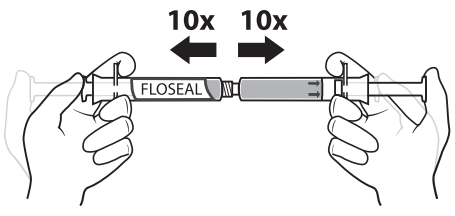
Mixing the Thrombin Solution into the Gelatin Matrix

- Remove and discard the Luer cap from the Gelatin Matrix Syringe, taking care to avoid spilling the Gelatin Matrix granules. Connect the two syringes.
- **Quickly** push the plunger of the **Thrombin solution syringe** to fully pass the solution into the Gelatin Matrix syringe and back again. This constitutes "one pass."
- **Rapidly** repeat this transfer for a total of 10 passes. It may take several passes for all the Gelatin Matrix granules to hydrate. Do not use excessive force to push the dry granules through the Luer connection during the first few passes as it may clog. **Ensure the syringe labeled FLOSEAL contains the FLOSEAL Matrix at the completion of mixing.**

Keep syringes connected until ready to use. Allow 30 seconds after preparation before product is applied to help ensure optimal product consistency and performance. To prevent premature drying of FLOSEAL Matrix, syringes can be kept connected until product is required.

FLOSEAL Matrix may be used up to eight (8) hours after mixing with the Thrombin solution.

When ready to use, remove the empty Thrombin solution syringe and discard appropriately. If desired, connect an Applicator tip to the FLOSEAL Matrix syringe. FLOSEAL Matrix may also be extruded directly from the syringe.



FLOSEAL Matrix Placement/Application Steps:

Do not inject FLOSEAL Matrix into blood vessels. See the Contraindications, Warnings, Precautions, and Adverse Events sections contained in these Instructions for Use.

For best results, FLOSEAL Matrix should be in complete contact with the actively bleeding tissue surface.

The particles of FLOSEAL Matrix swell approximately 10-20% upon contact with blood or other fluids. Maximum swell volume is achieved within about 10 minutes.

Application Technique

- Identify the source of bleeding at the tissue surface. This is the target site for FLOSEAL Matrix application.
- Manually approximate a gauze sponge moistened with sterile (non-heparinized) saline against the bleeding surface and use the Applicator tip (or syringe tip) to dispense FLOSEAL Matrix between the sponge and the bleeding surface. The gauze sponge will hold FLOSEAL Matrix in place against the bleeding surface in the presence of active bleeding. Apply enough FLOSEAL Matrix to create a small "mound" of material at the source of bleeding.
- For tissue defects ("divots" or "craters"), begin applying FLOSEAL Matrix at the deepest part of the lesion, and continue applying material as the syringe (or Applicator tip, if used) is withdrawn from the lesion. This "back-filling" action will ensure that FLOSEAL Matrix comes into contact with the entire bleeding surface at the tissue defect.
- Apply a gauze sponge moistened with sterile (non-heparinized) saline to approximate the FLOSEAL Matrix against the bleeding surface, conforming it to the lesion.
- After approximately two (2) minutes, lift the gauze sponge and inspect the wound site. Once bleeding has ceased, excess FLOSEAL Matrix (not incorporated in the hemostatic clot) should always be removed by gentle irrigation and suctioned away from the treatment site.
- To minimize disruption of the clot, remove gauze sponge after hemostasis has been achieved. If the gauze sponge adheres to the newly-formed clot, irrigate the sponge with non-heparinized saline and carefully remove it from the treated site.
- In cases of persistent bleeding, indicated by saturation and bleeding through the granules, insert the Applicator tip through the center of the mass of previously placed FLOSEAL Matrix to deliver fresh FLOSEAL Matrix as close as possible to the tissue surface. After re-application of FLOSEAL Matrix, resume approximation with a gauze sponge for up to another two (2) minutes, and then inspect the site again. Repeat re-application if necessary.
- If desired, dispense residual FLOSEAL Matrix from the tip using an equivalent amount of saline. Do not use air to apply the residual FLOSEAL Matrix.
- Once bleeding has ceased, excess FLOSEAL Matrix, material not incorporated in the hemostatic clot, should always be removed by gentle irrigation and suctioned out of the wound.
- Do not disrupt the FLOSEAL Matrix clot by physical manipulation. FLOSEAL Matrix incorporated in the hemostatic clot should be left *in situ*.
- After use, properly dispose of the FLOSEAL Matrix device with tip attached (if used).

Storage Conditions:

The FLOSEAL Matrix kit should be stored at 2 - 25°C (36 - 77°F). **Do not freeze.**

Symbols Referenced on Packaging

Symbol	Symbol Title / Decription	Standard and Symbol Number
 http://edocs.baxter.com	Consult instructions for use, eIFU indicator; Indicates the need for the user to consult the instructions for use and the instructions for use are available in an electronic format.	ISO 15223-1:2016, 5.4.3
	Do not inject into blood vessels; Indicates a medical device that should not be injected into blood vessels.	N/A
	Do not use if package is damaged; Indicates a medical device that should not be used if the package has been damaged or opened.	ISO 15223-1:2016, 5.2.8
	Sterilized using ethylene oxide; Indicates a medical device that has been sterilized using ethylene oxide.	ISO 15223-1:2016, 5.2.3
	Sterilized using irradiation; Indicates a medical device that has been sterilized using irradiation.	ISO 15223-1:2016, 5.2.4
	Temperature limit; Indicates the temperature limits to which the medical device can be safely exposed.	ISO 15223-1:2016, 5.3.7
	Do not re-use; Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure.	ISO 15223-1:2016, 5.4.2
	Catalogue number; Indicates the manufacturer's catalogue number so that the medical device can be identified.	ISO 15223-1:2016, 5.1.6
	Batch code; Indicates the manufacturer's batch code so that the batch or lot can be identified.	ISO 15223-1:2016, 5.1.5
	Use-by date; Indicates the date after which the medical device is not to be used.	ISO 15223-1:2016, 5.1.4
	Not made with natural rubber latex; Indicates the device is not made with natural rubber latex or dry natural rubber latex as a material of construction within the medical device or the packaging of a medical device.	ISO 15223-1:2016, 5.4.5 and Annex B, Section B2

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