

Instructions for Use for Configuration A

FloSeal™ Matrix Hemostatic Sealant Instructions for Use

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

DO NOT INJECT.

FloSeal™ Matrix Hemostatic Sealant must not be injected into blood vessels.

Device Description and Actions:

The FloSeal™ Matrix Hemostatic Sealant kit consists of a bovine-derived Gelatin Matrix, a bovine-derived Thrombin Component, an Applicator tip, and several mixing accessories. The mixing accessories include a syringe with a Dispersion Needle Assembly attached, a small bowl and a syringe with a needle attached. The mixing accessories are included to facilitate the reconstitution and dispersion of the thrombin into the Gelatin Matrix. The Applicator tip is included to facilitate the delivery of FloSeal™ Matrix Hemostatic Sealant to the site to be treated. (For specific kit contents, see Table in “How Supplied” section.) The Gelatin Matrix, manufactured by Fusion Medical Technologies, Inc. consists of crosslinked gelatin granules and is provided as a sterile hydrated gel in a standard disposable syringe. The Thrombin Component (Thrombin-JMI®), manufactured by Gentrac, Inc., contains sterile lyophilized Thrombin and sterile diluent (Sodium Chloride USP 0.9%). FloSeal™ Matrix is a combination of the Gelatin Matrix and the Thrombin Component. Thrombin must be added to the Gelatin Matrix prior to use. FloSeal™ Matrix is biocompatible, non-pyrogenic and resorbed within 6 to 8 weeks and can be left *in situ*, if desired.

Indications:

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

Contraindications:

Do not inject FloSeal™ Matrix into blood vessels or allow it to enter blood vessels. Extensive intravascular clotting and even death may result.

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.

Do not use FloSeal™ Matrix in patients with known allergies to materials of bovine origin.

See Contraindications in the Package Insert for Thrombin-JMI®.

Warnings:

- 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 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, reoperation may be necessary in order to remove the infected material and allow drainage.
- Regardless of the type of surgical procedure, surgeons should consider the maximum swell volume of approximately 20% of FloSeal™ Matrix after product is applied and its potential effect on the surrounding anatomic areas. Maximum swell volume is achieved within about 10 minutes.
- Excess FloSeal™ Matrix may be removed by gentle irrigation from the site of application when used in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm.
- The safety and effectiveness of FloSeal™ Matrix for use in neurosurgical, ophthalmic, and urological 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 and pregnant women.

WARNING

The use of topical bovine thrombin preparations has occasionally been associated with abnormalities in hemostasis ranging from asymptomatic alterations in laboratory determinations, such as prothrombin time (PT) and partial thromboplastin time (PTT), to severe bleeding or thrombosis which rarely have been fatal. These hemostatic effects appear to be related to the formation of antibodies against bovine thrombin and/or factor V which in some cases may cross react with human factor V, potentially resulting in factor V deficiency. Repeated clinical applications of topical bovine thrombin increases the likelihood that antibodies against thrombin and/or factor V may be formed. Consultation with an expert in coagulation disorders is recommended if a patient exhibits abnormal coagulation laboratory values, abnormal bleeding, or abnormal thrombosis following the use of topical thrombin. Any interventions should consider the immunologic basis of this condition. Patients with antibodies to bovine thrombin preparations should not be re-exposed to these products.

Precautions:

FloSeal™ Matrix Hemostatic Sealant is supplied as a sterile product for single use only. Do not resterilize.

When placed into cavities or closed tissue spaces, minimal preliminary compression is advised. When applied to a bleeding site, the particles of FloSeal™ Matrix swell approximately 20% upon contact with blood or other fluids. Maximum swell volume is achieved within about 10 minutes.

Once hemostasis is achieved, any excess FloSeal™ Matrix may be carefully removed by gentle irrigation.

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 40µ transfusion filters of blood scavenging systems.

FloSeal™ Matrix should not be used in conjunction with methylmethacrylate or other acrylic adhesives. 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.

See Precautions in the Package Insert for Thrombin-JMI® enclosed in the FloSeal™ Matrix Hemostatic Sealant kit.

Adverse Events:

In a randomized prospective, concurrently controlled clinical trial, 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 Patients. | | |
|---|------------------------|--|
| 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%) |
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| 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 known to be sensitive to bovine materials.

Other Gelatin-Based Hemostatic Agents: Reported Adverse Events:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- 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.

Adverse Reactions to Thrombin:

See Adverse Reactions in Package Insert for Thrombin-JMI® enclosed in the FloSeal™ Matrix Hemostatic Sealant kit.

Clinical Studies:

Study Design and Objectives: A prospective, randomized, controlled, multi-center, multi-specialty study was conducted. 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 Hemostatic Sealant, compared to a commercially available control hemostat, Absorbable Gelatin Sponge, U.S.P. (“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. Treatment 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 Treatment 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) | | |
|--|---|----------------|
| Patient Category | Median Time to Hemostasis in minutes (95% Confidence Interval [†]) | |
| | 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.

Immunology Results: Antibody data were available for 139 patients in the FloSeal™ Matrix group and 131 patients in the Control group. Twenty-five (25) patients (18%) in the FloSeal™ Matrix group and 26 patients (20%) in the Control group developed antibodies to bovine Thrombin ($p = 0.757$). Thirty-nine (39) patients (28%) in the FloSeal™ Matrix group and 43 patients (33%) in the Control group developed antibodies to bovine Factor V_a ($p = 0.428$). There was no evidence of any antibody-related coagulopathies, as judged by Prothrombin times, in any patients in the FloSeal™ Matrix or Control groups. At 6-8 weeks, 7 patients (5%) in the FloSeal™ Matrix group and 8 patients (6%) in the Control group, who were positive for either bovine thrombin or bovine Factor V_a antibodies, had elevated Prothrombin times (> 15 seconds). In each of these patients, the elevated Prothrombin time could primarily be attributed to prescribed anticoagulant medications.

Cross-reactivity to human thrombin was observed in five patients in the FloSeal™ Matrix group and three patients in the Control group. There was no statistically significant

difference between the two groups ($p = 0.455$, Fischer's Exact Test). There was no cross-reactivity to human Factor V_a in either the FloSeal™ Matrix or Control groups. Prothrombin times for all the patients in either group who tested positive for antibodies to human thrombin were within the normal limits for prothrombin time.

How Supplied:

FloSeal™ Matrix Hemostatic Sealant is provided in the configuration shown in the table below.

FloSeal™ Matrix Hemostatic Sealant Kit Configuration

| Gelatin Matrix Component | | | Thrombin Component |
|--------------------------|-----------------------|---|--|
| Size | Applicator Tip Length | Mixing Accessories | |
| 1 x 5 mL syringe | 1.0 inch | <ul style="list-style-type: none"> • 1 x 1 mL syringe with Dispersion Needle Assembly • 1 x bowl for Thrombin | <ul style="list-style-type: none"> • 1 x 5,000 Unit vial Thrombin • 1 x vial saline diluent, 5 mL • 1 x 1 mL syringe with needle attached |

The Kit includes the FloSeal™ Matrix Hemostatic Sealant Instructions for Use and a Thrombin-JMI® Package Insert.

Directions for Use:

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

FloSeal™ Matrix Hemostatic Sealant Preparation:

Inspect the integrity of the contents of the FloSeal™ Matrix Kit. If the packaging or vials have been damaged or opened, do not use.

Opening the kit

- Open the Thrombin Component package outside the sterile field. Items in this package will be used to reconstitute the Thrombin prior to transferring it to the sterile field.
- Open the outer package containing the Gelatin Matrix Component and deliver the sterile inner package to the sterile field. Once placed on the operating field, the inner package may be opened at any time.

Preparing the Thrombin solution

- Using the sterile 1 mL syringe provided in the Thrombin Component package, reconstitute the Thrombin powder using only 0.8 mL of sterile saline diluent. Discard the syringe and gently swirl the vial until the Thrombin is completely dissolved. Once reconstituted, the Thrombin solution should be used promptly. However, the solution may be refrigerated at 2-8°C for up to three hours.
- Remove the cap from the Thrombin vial and transfer the contents into the operating field by pouring the Thrombin solution into the small bowl provided in the Gelatin Matrix Component package. Alternatively, the Thrombin solution can be transferred to the small bowl with a syringe.

Loading Thrombin for delivery to the Gelatin Matrix

- Open the inner Gelatin Matrix Component package.
- Remove the sterile 1 mL syringe with Dispersion Needle Assembly.
- Ensure that the 1 mL syringe plunger is fully depressed.
- Place the blunt end of the dispersion needle into the Thrombin solution that has been poured into the bowl.
- Hold only the barrel of the 1 mL syringe and slowly and steadily press the barrel down into the pool of Thrombin solution. Allow the plunger of the 1 mL syringe to rise freely as the needle forces the plunger back and the syringe fills with Thrombin solution.
- Stop when the Luer connector contacts the bottom of the small bowl. If a small amount of air is aspirated, do not attempt to remove it. Keep the syringe pointed downward in order to check the volume. *If the volume of Thrombin solution is less than 0.5 mL, place the syringe tip in the bowl and dispense the Thrombin solution back into the bowl by slowly depressing the plunger. Repeat the loading process above.*
- Keep the syringe pointed downward, and depress plunger to the 0.5 mL mark. At this point, a small length of the dispersion needle should be protruding from the Luer connector of the assembly. Do not attempt to remove any air remaining in the syringe, as it is impossible and unnecessary.

Dispersing Thrombin Solution into the Gelatin Matrix

- Remove the Luer cap from the syringe containing the Gelatin Matrix.
- Connect the syringe containing the Thrombin solution to the syringe containing the Gelatin Matrix via the dispersion needle assembly. The protruding dispersion needle should be within the Gelatin Matrix.
- Steadily depress the plunger of the syringe containing the Thrombin solution to disperse the Thrombin solution throughout the Gelatin Matrix. Continue until the plunger of the syringe that contained Thrombin is fully depressed.
- After mixing the Gelatin Matrix and Thrombin, the FloSeal™ Matrix Hemostatic Sealant is now ready to use.

- Remove the Dispersion Needle Assembly, including the Luer connector and the 1 mL syringe and discard.
- If desired, connect an Applicator tip to the FloSeal™ Matrix syringe. FloSeal™ Matrix may also be extruded directly from the syringe.
- FloSeal™ Matrix may be used up to two (2) hours after mixing with the Thrombin solution.

FloSeal™ Matrix Placement/Application

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 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. A small amount of clear liquid may be expressed initially from the FloSeal™ Matrix syringe. 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 site of placement. A sufficient amount of material will ensure that the FloSeal™ Matrix is delivered directly to the site 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 enough direct pressure with a gauze sponge so that it holds the FloSeal™ Matrix against the bleeding surface and causes it to conform to the lesion.
- After approximately a minute (or two minutes if the patient has been heparinized), lift the gauze sponge and inspect the wound site. If bleeding has ceased, excess FloSeal™ Matrix may be removed by gentle irrigation.
- To minimize disruption of the clot, remove gauze sponges 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 direct pressure for another minute, and then inspect the site again. Repeat re-application if necessary.
- Once bleeding has ceased, excess FloSeal™ Matrix may be removed by gentle irrigation.
- Do not disrupt the FloSeal™ Matrix-clot complex by physical manipulation. FloSeal™ Matrix may be left *in situ* whenever necessary.

The FloSeal™ Matrix Hemostatic Sealant Kit should be stored at 2 - 25°C (36 - 77°F). Refrigeration is not necessary.

If refrigerated, for optimum ease of use remove FloSeal™ Matrix Hemostatic Sealant Kit from the refrigerator prior to the start of the surgical case. Any unopened kits may be returned to the refrigerator.

Manufactured by:
Fusion Medical Technologies, Inc.
Mountain View, Ca 94043, USA
(650) 903 4000

Label code: Rev: Rev. Date:

Instructions for Use for Configuration B

FloSeal™ Matrix Hemostatic Sealant Instructions for Use

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

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Contraindications:

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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.

Do not use FloSeal™ Matrix in patients with known allergies to materials of bovine origin.

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| 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 known to be sensitive to bovine materials.

Other Gelatin-Based Hemostatic Agents: Reported Adverse Events:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- 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.

Adverse Reactions to Thrombin:

See Adverse Reactions in Package Insert for Thrombin-JMI® enclosed in the FloSeal™ Matrix Hemostatic Sealant kit.

Clinical Studies:

Study Design and Objectives: A prospective, randomized, controlled, multi-center, multi-specialty study was conducted. 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 Hemostatic Sealant, compared to a commercially available control hemostat, Absorbable Gelatin Sponge, U.S.P. (“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. Treatment 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 Treatment 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) | | |
|--|--|----------------|
| Patient Category | Median Time to Hemostasis in minutes (95% Confidence Interval*) | |
| | 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.

Immunology Results: Antibody data were available for 139 patients in the FloSeal™ Matrix group and 131 patients in the Control group. Twenty-five (25) patients (18%) in the FloSeal™ Matrix group and 26 patients (20%) in the Control group developed antibodies to bovine Thrombin ($p = 0.757$). Thirty-nine (39) patients (28%) in the FloSeal™ Matrix group and 43 patients (33%) in the Control group developed antibodies to bovine Factor V_a ($p = 0.428$). There was no evidence of any antibody-related coagulopathies, as judged by Prothrombin times, in any patients in the FloSeal™ Matrix or Control groups. At 6-8 weeks, 7 patients (5%) in the FloSeal™ Matrix group and 8 patients (6%) in the Control group, who were positive for either bovine thrombin or bovine Factor V_a antibodies, had elevated Prothrombin times (> 15 seconds). In each of these patients, the elevated Prothrombin time could primarily be attributed to prescribed anticoagulant medications.

Cross-reactivity to human thrombin was observed in five patients in the FloSeal™ Matrix group and three patients in the Control group. There was no statistically significant

difference between the two groups ($p = 0.455$, Fischer's Exact Test). There was no cross-reactivity to human Factor V_a in either the FloSeal™ Matrix or Control groups. Prothrombin times for all the patients in either group who tested positive for antibodies to human thrombin were within the normal limits for prothrombin time.

How Supplied:

FloSeal™ Matrix Hemostatic Sealant is provided in the configuration shown in the table below.

FloSeal™ Matrix Hemostatic Sealant Kit Configuration

| Gelatin Matrix Component | | | Thrombin Component |
|--------------------------|-----------------------|---|--|
| Size | Applicator Tip Length | Mixing Accessories | |
| 2 x 5 mL syringe | 1 inch | <ul style="list-style-type: none"> • 1 x 1 mL syringe with Dispersion Needle Assembly • 1 x bowl for Thrombin | <ul style="list-style-type: none"> • 1 x 10,000 Unit vial Thrombin • 1 x vial saline diluent, 10 mL • 1 x 3 mL syringe with needle attached |

The Kit includes the FloSeal™ Matrix Hemostatic Sealant Instructions for Use and a Thrombin-JMI® Package Insert.

Directions for Use:

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

FloSeal™ Matrix Hemostatic Sealant Preparation:

Inspect the integrity of the contents of the FloSeal™ Matrix Kit. If the packaging or vials have been damaged or opened, do not use.

Opening the kit

- Open the Thrombin Component package outside the sterile field. Items in this package will be used to reconstitute the Thrombin prior to transferring it to the sterile field.
- Open the outer package containing the Gelatin Matrix Component and deliver the sterile inner package to the sterile field. Once placed on the operating field, the inner package may be opened at any time.

Preparing the Thrombin solution

- Using the sterile 3 mL syringe provided in the Thrombin Component package, reconstitute the Thrombin powder using only 1.6 mL of sterile saline diluent. Discard the syringe and gently swirl the vial until the Thrombin is completely dissolved. Once reconstituted, the Thrombin solution should be used promptly. However, the solution may be refrigerated at 2-8°C for up to three hours.
- Remove the cap from the Thrombin vial and transfer the contents into the operating field by pouring the Thrombin solution into the small bowl provided in the Gelatin Matrix Component package. Alternatively, the Thrombin solution can be transferred to the small bowl with a syringe.

Loading Thrombin for delivery to the Gelatin Matrix

- Open the inner Gelatin Matrix Component package.
- Remove the sterile 1 mL syringe with Dispersion Needle Assembly.
- Ensure that the 1 mL syringe plunger is fully depressed.
- Place the blunt end of the dispersion needle into the Thrombin solution that has been poured into the bowl.
- Hold only the barrel of the 1 mL syringe and slowly and steadily press the barrel down into the pool of Thrombin solution. Allow the plunger of the 1 mL syringe to rise freely as the needle forces the plunger back and the syringe fills with Thrombin solution.
- Stop when the Luer connector contacts the bottom of the small bowl. If a small amount of air is aspirated, do not attempt to remove it. Keep the syringe pointed downward in order to check the volume. *If the volume of Thrombin solution is less than 0.5 mL, place the syringe tip in the bowl and dispense the Thrombin solution back into the bowl by slowly depressing the plunger. Repeat the loading process above.*
- Keep the syringe pointed downward, and depress plunger to the 0.5 mL mark. At this point, a small length of the dispersion needle should be protruding from the Luer connector of the assembly. Do not attempt to remove any air remaining in the syringe, as it is impossible and unnecessary.

Dispersing Thrombin Solution into the Gelatin Matrix

- Remove the Luer cap from the syringe containing the Gelatin Matrix.
- Connect the syringe containing the Thrombin solution to the syringe containing the Gelatin Matrix via the dispersion needle assembly. The protruding dispersion needle should be within the Gelatin Matrix.
- Steadily depress the plunger of the syringe containing the Thrombin solution to disperse the Thrombin solution throughout the Gelatin Matrix. Continue until the plunger of the syringe that contained Thrombin is fully depressed.
- After mixing the Gelatin Matrix and Thrombin, the FloSeal™ Matrix Hemostatic Sealant is now ready to use.

- Remove the Dispersion Needle Assembly, including the Luer connector and the 1 mL syringe.
- Immediately reload the 1 mL syringe/dispersion needle assembly with the remaining Thrombin solution as in steps “Loading Thrombin for delivery to the Gelatin Matrix”.
- Repeat the steps for dispersing the Thrombin solution into the second Gelatin Matrix syringe.
- If desired, connect an Applicator tip to the FloSeal™ Matrix syringe. FloSeal™ Matrix may also be extruded directly from the syringe.
- FloSeal™ Matrix may be used up to two (2) hours after mixing with the Thrombin solution.

FloSeal™ Matrix Placement/Application

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 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. A small amount of clear liquid may be expressed initially from the FloSeal™ Matrix syringe. 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 site of placement. A sufficient amount of material will ensure that the FloSeal™ Matrix is delivered directly to the site 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 enough direct pressure with a gauze sponge so that it holds the FloSeal™ Matrix against the bleeding surface and causes it to conform to the lesion.

- After approximately a minute (or two minutes if the patient has been heparinized), lift the gauze sponge and inspect the wound site. If bleeding has ceased, excess FloSeal™ Matrix may be removed by gentle irrigation.
- To minimize disruption of the clot, remove gauze sponges 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 direct pressure for another minute, and then inspect the site again. Repeat re-application if necessary.
- Once bleeding has ceased, excess FloSeal™ Matrix may be removed by gentle irrigation.
- Do not disrupt the FloSeal™ Matrix-clot complex by physical manipulation. FloSeal™ Matrix may be left *in situ* whenever necessary.

The FloSeal™ Matrix Hemostatic Sealant Kit should be stored at 2 - 25°C (36 - 77°F). Refrigeration is not necessary.

If refrigerated, for optimum ease of use remove FloSeal™ Matrix Hemostatic Sealant Kit from the refrigerator prior to the start of the surgical case. Any unopened kits may be returned to the refrigerator.

Manufactured by:
Fusion Medical Technologies, Inc.
Mountain View, Ca 94043, USA
(650) 903 4000

Label code: Rev: Rev. Date:

Instructions for Use for Configuration C

FloSeal™ Matrix Hemostatic Sealant Instructions for Use

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

DO NOT INJECT.

FloSeal™ Matrix Hemostatic Sealant must not be injected into blood vessels.

Device Description and Actions:

The FloSeal™ Matrix Hemostatic Sealant kit consists of a bovine-derived Gelatin Matrix, a bovine-derived Thrombin Component, an Applicator tip, and several mixing accessories. The mixing accessories include a syringe with a Dispersion Needle Assembly attached, a small bowl, and a syringe with a needle attached. The mixing accessories are included to facilitate the reconstitution and dispersion of the thrombin into the Gelatin Matrix. The Applicator tip is included to facilitate the delivery of FloSeal™ Matrix Hemostatic Sealant to the site to be treated. (For specific kit contents, see Table in “How Supplied” section.) The Gelatin Matrix, manufactured by Fusion Medical Technologies, Inc. consists of crosslinked gelatin granules and is provided as a sterile hydrated gel in a standard disposable syringe. The Thrombin Component (Thrombin-JMI®), manufactured by Gentrac, Inc., contains sterile lyophilized Thrombin and sterile diluent (Sodium Chloride USP 0.9%). FloSeal™ Matrix is a combination of the Gelatin Matrix and the Thrombin Component. Thrombin must be added to the Gelatin Matrix prior to use. FloSeal™ Matrix is biocompatible, non-pyrogenic and resorbed within 6 to 8 weeks and can be left *in situ*, if desired.

Indications:

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

Contraindications:

Do not inject FloSeal™ Matrix into blood vessels or allow it to enter blood vessels. Extensive intravascular clotting and even death may result.

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.

Do not use FloSeal™ Matrix in patients with known allergies to materials of bovine origin.

See Contraindications in the Package Insert for Thrombin-JMI®.

Warnings:

- 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 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, reoperation may be necessary in order to remove the infected material and allow drainage.
- Regardless of the type of surgical procedure, surgeons should consider the maximum swell volume of approximately 20% of FloSeal™ Matrix after product is applied and its potential effect on the surrounding anatomic areas. Maximum swell volume is achieved within about 10 minutes.
- Excess FloSeal™ Matrix may be removed by gentle irrigation from the site of application when used in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm.
- The safety and effectiveness of FloSeal™ Matrix for use in neurosurgical, ophthalmic, and urological 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 and pregnant women.

WARNING

The use of topical bovine thrombin preparations has occasionally been associated with abnormalities in hemostasis ranging from asymptomatic alterations in laboratory determinations, such as prothrombin time (PT) and partial thromboplastin time (PTT), to severe bleeding or thrombosis which rarely have been fatal. These hemostatic effects appear to be related to the formation of antibodies against bovine thrombin and/or factor V which in some cases may cross react with human factor V, potentially resulting in factor V deficiency. Repeated clinical applications of topical bovine thrombin increases the likelihood that antibodies against thrombin and/or factor V may be formed. Consultation with an expert in coagulation disorders is recommended if a patient exhibits abnormal coagulation laboratory values, abnormal bleeding, or abnormal thrombosis following the use of topical thrombin. Any interventions should consider the immunologic basis of this condition. Patients with antibodies to bovine thrombin preparations should not be re-exposed to these products.

Precautions:

FloSeal™ Matrix Hemostatic Sealant is supplied as a sterile product for single use only. Do not resterilize.

When placed into cavities or closed tissue spaces, minimal preliminary compression is advised. When applied to a bleeding site, the particles of FloSeal™ Matrix swell approximately 20% upon contact with blood or other fluids. Maximum swell volume is achieved within about 10 minutes.

Once hemostasis is achieved, any excess FloSeal™ Matrix may be carefully removed by gentle irrigation.

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 40µ transfusion filters of blood scavenging systems.

FloSeal™ Matrix should not be used in conjunction with methylmethacrylate or other acrylic adhesives. 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.

See Precautions in the Package Insert for Thrombin-JMI® enclosed in the FloSeal™ Matrix Hemostatic Sealant kit.

Adverse Events:

In a randomized prospective, concurrently controlled clinical trial, 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 Patients. | | |
|---|------------------------|--|
| 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 known to be sensitive to bovine materials.

Other Gelatin-Based Hemostatic Agents: Reported Adverse Events:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- 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.

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Clinical Studies:

Study Design and Objectives: A prospective, randomized, controlled, multi-center, multi-specialty study was conducted. 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 Hemostatic Sealant, compared to a commercially available control hemostat, Absorbable Gelatin Sponge, U.S.P. (“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. Treatment 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 Treatment 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:

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| Hemostasis Success at 10 Minutes Before and After Protamine Administration (Cardiac Patients Only) | | |
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| 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) | | |
|--|---|----------------|
| Patient Category | Median Time to Hemostasis in minutes (95% Confidence Interval) | |
| | 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.

Immunology Results: Antibody data were available for 139 patients in the FloSeal™ Matrix group and 131 patients in the Control group. Twenty-five (25) patients (18%) in the FloSeal™ Matrix group and 26 patients (20%) in the Control group developed antibodies to bovine Thrombin ($p = 0.757$). Thirty-nine (39) patients (28%) in the FloSeal™ Matrix group and 43 patients (33%) in the Control group developed antibodies to bovine Factor V_a ($p = 0.428$). There was no evidence of any antibody-related coagulopathies, as judged by Prothrombin times, in any patients in the FloSeal™ Matrix or Control groups. At 6-8 weeks, 7 patients (5%) in the FloSeal™ Matrix group and 8 patients (6%) in the Control group, who were positive for either bovine thrombin or bovine Factor V_a antibodies, had elevated Prothrombin times (> 15 seconds). In each of these patients, the elevated Prothrombin time could primarily be attributed to prescribed anticoagulant medications.

Cross-reactivity to human thrombin was observed in five patients in the FloSeal™ Matrix group and three patients in the Control group. There was no statistically significant

difference between the two groups ($p = 0.455$, Fischer's Exact Test). There was no cross-reactivity to human Factor V_a in either the FloSeal™ Matrix or Control groups. Prothrombin times for all the patients in either group who tested positive for antibodies to human thrombin were within the normal limits for prothrombin time.

How Supplied:

FloSeal™ Matrix Hemostatic Sealant is provided in the configuration shown in the table below.

FloSeal™ Matrix Hemostatic Sealant Kit Configuration

| Gelatin Matrix Component | | | Thrombin Component |
|--------------------------|-----------------------|---|--|
| Size | Applicator Tip Length | Mixing Accessories | |
| 1 x 5 mL syringe | 2.5 inches | <ul style="list-style-type: none"> • 1 x 1 mL syringe with Dispersion Needle Assembly • 1 x bowl for Thrombin | <ul style="list-style-type: none"> • 1 x 5,000 Unit vial Thrombin • 1 x vial saline diluent, 5 mL • 1 x 1 mL syringe with needle attached |

The Kit includes the FloSeal™ Matrix Hemostatic Sealant Instructions for Use and a Thrombin-JMI® Package Insert.

Directions for Use:

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

FloSeal™ Matrix Hemostatic Sealant Preparation:

Inspect the integrity of the contents of the FloSeal™ Matrix Kit. If the packaging or vials have been damaged or opened, do not use.

Opening the kit

- Open the Thrombin Component package outside the sterile field. Items in this package will be used to reconstitute the Thrombin prior to transferring it to the sterile field.
- Open the outer package containing the Gelatin Matrix Component and deliver the sterile inner package to the sterile field. Once placed on the operating field, the inner package may be opened at any time.

Preparing the Thrombin solution

- Using the sterile 1 mL syringe provided in the Thrombin Component package, reconstitute the Thrombin powder using only 0.8 mL of sterile saline diluent. Discard the syringe and gently swirl the vial until the Thrombin is completely dissolved. Once reconstituted, the Thrombin solution should be used promptly. However, the solution may be refrigerated at 2-8°C for up to three hours.
- Remove the cap from the Thrombin vial and transfer the contents into the operating field by pouring the Thrombin solution into the small bowl provided in the Gelatin Matrix Component package. Alternatively, the Thrombin solution can be transferred to the small bowl with a syringe.

Loading Thrombin for delivery to the Gelatin Matrix

- Open the inner Gelatin Matrix Component package.
- Remove the sterile 1 mL syringe with Dispersion Needle Assembly.
- Ensure that the 1 mL syringe plunger is fully depressed.
- Place the blunt end of the dispersion needle into the Thrombin solution that has been poured into the bowl.
- Hold only the barrel of the 1 mL syringe and slowly and steadily press the barrel down into the pool of Thrombin solution. Allow the plunger of the 1 mL syringe to rise freely as the needle forces the plunger back and the syringe fills with Thrombin solution.
- Stop when the Luer connector contacts the bottom of the small bowl. If a small amount of air is aspirated, do not attempt to remove it. Keep the syringe pointed downward in order to check the volume. *If the volume of Thrombin solution is less than 0.5 mL, place the syringe tip in the bowl and dispense the Thrombin solution back into the bowl by slowly depressing the plunger. Repeat the loading process above.*
- Keep the syringe pointed downward, and depress plunger to the 0.5 mL mark. At this point, a small length of the dispersion needle should be protruding from the Luer connector of the assembly. Do not attempt to remove any air remaining in the syringe, as it is impossible and unnecessary.

Dispersing Thrombin Solution into the Gelatin Matrix

- Remove the Luer cap from the syringe containing the Gelatin Matrix.
- Connect the syringe containing the Thrombin solution to the syringe containing the Gelatin Matrix via the dispersion needle assembly. The protruding dispersion needle should be within the Gelatin Matrix.
- Steadily depress the plunger of the syringe containing the Thrombin solution to disperse the Thrombin solution throughout the Gelatin Matrix. Continue until the plunger of the syringe that contained Thrombin is fully depressed.
- After mixing the Gelatin Matrix and Thrombin, the FloSeal™ Matrix Hemostatic Sealant is now ready to use.

- Remove the Dispersion Needle Assembly, including the Luer connector and the 1 mL syringe and discard.
- If desired, connect an Applicator tip to the FloSeal™ Matrix syringe. FloSeal™ Matrix may also be extruded directly from the syringe.
- FloSeal™ Matrix may be used up to two (2) hours after mixing with the Thrombin solution.

FloSeal™ Matrix Placement/Application

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 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. A small amount of clear liquid may be expressed initially from the FloSeal™ Matrix syringe. 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 site of placement. A sufficient amount of material will ensure that the FloSeal™ Matrix is delivered directly to the site 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 enough direct pressure with a gauze sponge so that it holds the FloSeal™ Matrix against the bleeding surface and causes it to conform to the lesion.
- After approximately a minute (or two minutes if the patient has been heparinized), lift the gauze sponge and inspect the wound site. If bleeding has ceased, excess FloSeal™ Matrix may be removed by gentle irrigation.
- To minimize disruption of the clot, remove gauze sponges 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 direct pressure for another minute, and then inspect the site again. Repeat re-application if necessary.
- Once bleeding has ceased, excess FloSeal™ Matrix may be removed by gentle irrigation.
- Do not disrupt the FloSeal™ Matrix-clot complex by physical manipulation. FloSeal™ Matrix may be left *in situ* whenever necessary.

The FloSeal™ Matrix Hemostatic Sealant Kit should be stored at 2 - 25°C (36 - 77°F). Refrigeration is not necessary.

If refrigerated, for optimum ease of use remove FloSeal™ Matrix Hemostatic Sealant Kit from the refrigerator prior to the start of the surgical case. Any unopened kits may be returned to the refrigerator.

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Label code: Rev: Rev. Date: