CRYOSEAL® FS SYSTEM

INSTRUCTIONS FOR USE

- Intended for the preparation of fibrin sealant from a unit of **autologous plasma** in a closed, sterile fluid path

DESCRIPTION
The CryoSeal Fibrin Sealant (FS) System is a medical device that simultaneously produces cryoprecipitate and thrombin from a unit of autologous plasma. When components are mixed they form a fibrin sealant for use in liver resection surgery as an adjunct to hemostasis.

COMPONENTS
- **CryoSeal Instrument (CS-1)**
  The CS-1 instrument is a compact floor standing device which utilizes the specially designed CP-3 plasma processing disposable to produce the fibrin sealant components.
- **CP-3 Disposable**
  The CP-3 Disposable is a sterile, single use kit containing thrombin and cryoprecipitate processing chambers and four (4) individually overwrapped sterile dual syringe sets that allow for collection and storage of the fibrin sealant components.
- **Thrombin Processing Chamber Reagent**
  The Thrombin Processing Chamber reagent comprises Ethanol, 66.6% (v/v), USP, and 25 millimolar Calcium Chloride. The reagent is terminally sterilized using steam sterilization and then placed into an overwrap pouch.
- **Applicator System**
  The FS Applicator System consists of a dispensing handle and various spray or line drop tips for use with FS syringe sets.
- **The Warming Tray**
  The FS Warming Tray is designed to hold assembled FS syringe sets and warm the fibrin sealant components to 34-37^{o}C, prior to use.
- **The Harvest Rack**
  The Harvest Rack is an accessory on which the CP-3 is placed during harvesting of the cryoprecipitate and thrombin components into the overwrapped syringe sets.
- **Source of Plasma**
  To be used with **autologous plasma** only.

PLEASE REFER TO OPERATOR'S MANUAL FOR DETAILED DIRECTIONS FOR USE.

INDICATIONS
The CryoSeal FS System is intended for the preparation of fibrin sealant from a unit of autologous plasma in a closed, sterile fluid path. The autologous fibrin sealant is indicated for use as an adjunct to hemostasis on the incised liver surface in patients undergoing liver resection when control of bleeding by standard surgical techniques is ineffective or impractical.

CONTRAINDICATIONS
- **Do not inject prepared fibrin sealant into a vessel.**
- **Do not use for the treatment of severe or brisk arterial bleeding**.
- **Excluded from autologous donation of blood for eventual use with the CryoSeal FS System: Patients with hereditary or acquired hematologic/coagulation disorders e.g. (a) sickle cell anemia, (b) von Willebrand disease, (c) coagulation factor deficiencies including: prothrombin, Factor V, Factor VII, Factor VIII (hemophilia A), Factor IX (hemophilia B), Factor X, Factor XI, Factor XII, Factor XIII, (d) afibrinogenemia or dysfibrinogenemia, (e) disseminated intravascular coagulation or (f) disorders of plasma viscosity (e.g., Waldenstrom's macroglobulinemia, multiple myeloma, hyperlipidemia).**

- **Use of anticoagulant therapy including coumadin and heparin within 7 days of surgery or aspirin or antiplatelet agents (including nonsteroidal anti-inflammatory medications) within 48 hours of surgery.**

WARNINGS

- Potential Biohazardous Material: All technicians operating the CryoSeal FS System must be trained in the proper handling and disposal of blood byproducts and biohazardous waste in a biohazardous waste container in accordance with appropriate regulations.
- The CryoSeal Instrument (CS-1) must not be used in the operating room.

PRECAUTIONS

- For protection against electrical shock hazards, the CS-1 must be plugged into a properly grounded electrical source by a qualified electrician.
- If the CryoSeal FS System is used in a manner not specified by the manufacturer, the protection provided by the equipment may be impaired.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A total of 100 patients were treated with fibrin sealant produced with the CryoSeal FS System and 53 patients were treated with collagen absorbable hemostatic device, INSTAT, during the multi-center clinical trial. The most common adverse events recorded during and after application of the fibrin sealant were: pain, nausea, fever, abdominal pain, constipation, gastrointestinal disorder, anemia, and hypertension. The following adverse events were observed in > 1% of treated patients.

Adverse Event	Fibrin Sealant	Collagen Absorbable
Pain	69 (69.0%)	38 (71.7%)
Nausea	38 (38.0%)	21 (39.6%)
Fever	36 (36.0%)	20 (37.7%)
Abdominal Pain	30 (30.0%)	7 (13.2%)
Constipation	28 (28.0%)	20 (37.7%)
Anemia	24 (24.0%)	10 (18.9%)
Gastrointestinal Disorder	24 (24.0%)	10 (18.9%)
Hypertension	22 (22.0%)	5 (9.4%)
Hypokalemia	17 (17.0%)	6 (11.3%)
Hyperglycemia	16 (16.0%)	10 (18.9%)
Pruritus	16 (16.0%)	10 (18.9%)
Generalized Edema	14 (14.0%)	3 (5.7%)
Vomiting	14 (14.0%)	9 (17.0%)
Asthenia	13 (13.0%)	5 (9.4%)
Diarrhea	11 (11.0%)	5 (9.4%)
Hypophosphatemia	11 (11.0%)	5 (9.4%)
Lung Disorder	11 (11.0%)	8 (15.1%)
Tachycardia	11 (11.0%)	6 (11.3%)
Insomnia	10 (10.0%)	10 (18.9%)
Hypomagnesemia	9 (9.0%)	5 (9.4%)
Dyspnea	8 (8.0%)	4 (7.5%)
Flatulence	8 (8.0%)	4 (7.5%)
Hypotension	8 (8.0%)	3 (5.7%)
Infection	7 (7.0%)	5 (9.4%)
Oliguria	7 (7.0%)	8 (15.1%)
Peripheral Edema	7 (7.0%)	7 (13.2%)
Cough Increased	6 (6.0%)	6 (11.3%)
Dyspepsia	6 (6.0%)	7 (13.2%)
Edema	6 (6.0%)	6 (11.3%)
Rash	6 (6.0%)	4 (7.5%)
Atelectasis	5 (5.0%)	3 (5.7%)
Dizziness	5 (5.0%)	3 (5.7%)
Hypocalcemia	5 (5.0%)	0
Abdomen Enlarged	4 (4.0%)	7 (13.2%)
Agitation	4 (4.0%)	0
Anorexia	4 (4.0%)	1 (1.9%)
Chest Pain	4 (4.0%)	2 (3.8%)
Ileus	4 (4.0%)	1 (1.9%)

Adverse Event	Fibrin Sealant	Collagen Absorbable
Injection Site Reaction	4 (4.0%)	2 (3.8%)
Liver Function Tests-Abnormal	4 (4.0%)	0
Pleural Effusion	4 (4.0%)	4 (7.5%)
Urinary Tract Infection	4 (4.0%)	4 (7.5%)
Anxiety	3 (3.0%)	1 (1.9%)
Ascites	3 (3.0%)	3 (5.7%)
Back Pain	3 (3.0%)	5 (9.4%)
Confusion	3 (3.0%)	0
Gastrointestinal Hemorrhage	3 (3.0%)	0
Headache	3 (3.0%)	3 (5.7%)
Lactic Acidosis	3 (3.0%)	0
Pneumonia	3 (3.0%)	1 (1.9%)
Pneumothorax	3 (3.0%)	1 (1.9%)
Prothrombin Decreased	3 (3.0%)	1 (1.9%)
Respiratory Acidosis	3 (3.0%)	2 (3.8%)
Thromboplastin Decreased	3 (3.0%)	1 (1.9%)
Acidosis	2 (2.0%)	0
Asthma	2 (2.0%)	3 (5.7%)
Depression	2 (2.0%)	2 (3.8%)
Dry Eyes	2 (2.0%)	0
Dysphagia	2 (2.0%)	1 (1.9%)
Ecchymosis	2 (2.0%)	1 (1.9%)
Healing Abnormal	2 (2.0%)	1 (1.9%)
Hematuria	2 (2.0%)	1 (1.9%)
Hemorrhage	2 (2.0%)	3 (5.7%)
Hiccup	2 (2.0%)	1 (1.9%)
Hypertonia	2 (2.0%)	0
Hyperventilation	2 (2.0%)	0
Hypesthesia	2 (2.0%)	1 (1.9%)
Hyponatremia	2 (2.0%)	2 (3.8%)
Hypovolemia	2 (2.0%)	1 (1.9%)
Hypoxia	2 (2.0%)	0
Infection Bacterial	2 (2.0%)	0
Injection Site Pain	2 (2.0%)	2 (3.8%)
Lab Test Abnormal	2 (2.0%)	0
Migraine	2 (2.0%)	0
Nausea and Vomiting	2 (2.0%)	2 (3.8%)
Pharyngitis	2 (2.0%)	3 (5.7%)
Stupor	2 (2.0%)	0
Thinking Abnormal	2 (2.0%)	1 (1.9%)
Urinary Retention	2 (2.0%)	0

Patients are counted once for each preferred term. Adverse events are coded to preferred term using the COSTART dictionary, version 5.0.

Other adverse events observed in 1% or fewer of the fibrin sealant treated patients were: abscess, accidental injury, alkalosis, anaphylactoid reaction, arthritis, AV block, bradycardia, cellulitis, cerebrovascular accident, chills, congestive heart failure, conjunctivitis, eructation, glycosuria, hemoptysis, herpes zoster, hypercholesterolemia, hyperphosphatemia, hypertension, hypervolemia, hypothyroidism, injection site inflammation, lung edema, maculopapular rash, malaise, mouth ulceration, neuropathy, paresthesia, peripheral neuritis, polyuria, pulmonary embolus, rectal disorder, respiratory disorder, shock, skin disorder, sweating, urinary incontinence, urine abnormality, ventricular extrasystoles, vertigo, withdrawal syndrome, delusions.

CLINICAL STUDY

Study Objectives: To investigate the efficacy and safety of autologous fibrin sealant prepared by the CryoSeal FS System in terminating bleeding at the margin of a hepatic resection during liver resection surgery.

Study Design: A total of 153 patients at 13 clinical sites were randomized into two study groups: (1) control using collagen absorbable hemostatic device, INSTAT or (2) fibrin sealant prepared with the CryoSeal FS System. Both products were used to control bleeding from the incised hepatic surface. Of the 153 randomized patients, 118 were evaluated for effectiveness. Of those 118 patients, 77 patients

were randomized to the autologous fibrin sealant study group and 41 patients were randomized to the control group. All 153 patients were evaluated for safety. All study personnel were blinded to the treatment group until immediately prior to beginning the adjunct to hemostasis treatment (T3) with the study product or control. Each patient was followed for 30±3 days post-operatively.

Study Endpoints: The primary endpoint was time to hemostasis determined from the time of product application to the time when hemostasis was obtained. Secondary endpoints included: (1) percent success in achieving hemostasis within 10 minutes of first application, (2) intra-operative blood/fluid loss, (3) blood loss in drainage bag, (4) transfusion requirements, (5) re-operation due to bleeding.

Study Results:

- **Primary Efficacy Endpoint:**
  Median time to hemostasis was 3.48 minutes for the CryoSeal FS group compared to 6.67 minutes for the control group. Mean time to hemostasis was 4.84 minutes for the CryoSeal FS group compared to 7.60 minutes for the control group. This difference was statistically significant ($p<0.001$).

- **Secondary Efficacy Endpoints:**
  Hemostasis within 10 minutes: 94.8% of patients in the CryoSeal FS group and 75.6% of patients in the control group achieved hemostasis within 10 minutes.

  Intraoperative blood/fluid loss: The mean intraoperative blood/fluid loss between T3 and T4 was not different between control and CryoSeal FS groups.

  Blood loss in drainage bag: The post-operative blood loss in drainage bag using the Associate Clinical Data Imputation Methods demonstrated that there were no clinically or statistically significant differences between control and CryoSeal FS groups.

  Transfusion requirements: The need for transfusion was not statistically significant between the two study groups, 72.7% for the CryoSeal FS group compared to 75.6% for the control group.

  Re-operation due to bleeding: The need for re-operation due to bleeding was not statistically different between the two study groups, 2.6% for the CryoSeal FS group compared to 0% for the control group. The need for re-operation was unrelated to the application of the fibrin sealant.

STORAGE CONDITIONS

Components may be stored up to 6 hours at 34-37^{o}C (93-98^{o}F) or on ice for up to 4 hours, with 2 additional hours at 34-37^{o}C (93-98^{o}F). Components should be prewarmed for at least 10 minutes prior to use. DO NOT STORE AT ROOM TEMPERATURE.

CryoSeal and related technologies are protected by the following U.S. patents:
5,261,255, 5,520,885, 5,750,658, 5,759,171, 5,939,023, 5,975,367, 6,077,447, 6,274,090 B1, 6,472,162 B1, 6,679,300 B1, 6,808,675 B1, 7,056,722, 7,182,107

The technologies are also protected by international intellectual property agencies.

PRODUCT APPLICATION
The FS Applicator System is assembled using the steps in Figures 1-4 and applied using the following application instructions.

Figure 1: Attach tip manifold to dispensing handle.

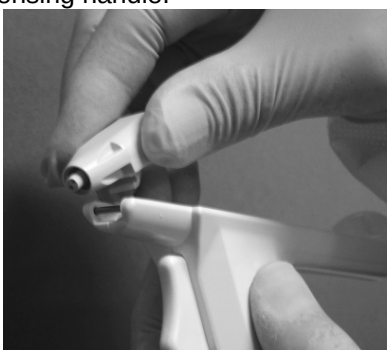


Figure 2: Insert syringe set into tip manifold.

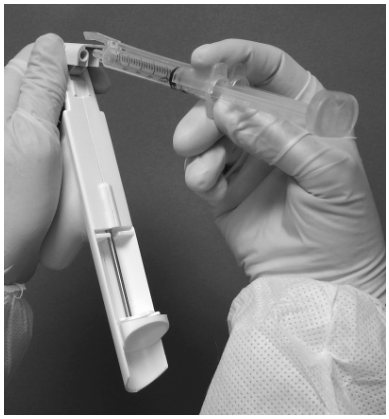


Figure 3: Attach desired spray or line/drop tip to tip manifold *(shown with ST-3 spray tip).*

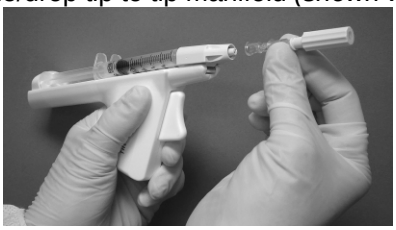
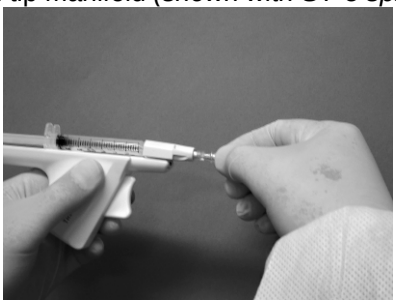


Figure 4: Twist tip into luer fitting on tip manifold *(shown with ST-3 spray tip).*



Apply using techniques outlined in the following section.

Application Using Spray Tip (ST-2,3,4):

1) Hold the FS Applicator so that the tip is pointing toward the area targeted for hemostasis.
2) Position tip approximately 3 inches from the surface of the target, depending on whether a small, focused spray or a broad, fine mist spray is desired. Move applicator closer to target for more concentrated spray or to cover a smaller surface area. Move applicator away from target for broader surface coverage and finer spray.
3) For metered application, squeeze firmly on the trigger of the handle while moving the hand in an "air brushing" back and forth type motion. For non-metered application, simultaneously depress plungers on the syringe set while moving the hand back and forth using the side-to-side "air brush" motion.

Application Using Line/Drop Tip (DT-5,10):

1) Hold FS Applicator such that the tip is pointing toward the area targeted for hemostasis.
2) Position the tip approximately 0.25 inches from the surface of the target.
3) For metered application, squeeze the trigger of the handle to deliver fibrin sealant to the surgical target. For non-metered application, simultaneously depress plungers on syringe set to deliver the sealant. The single cannula allows for mixing of sealant prior to application.