Section 2

SUMMARY OF SAFETY AND EFFECTIVENESS

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- **Intended for the preparation of fibrin sealant from a unit of autologous plasma in a closed, sterile fluid path**
- **Exclude individuals with hereditary or acquired hematologic/coagulation disorders and disorders of plasma viscosity.**

I. GENERAL INFORMATION:

DEVICE TRADE NAME: CryoSeal FS System

APPLICANT: ThermoGenesis Corp.
2711 Citrus Road
Rancho Cordova, CA 95742

PMA NUMBER: BP060001

DATE OF PANEL: None

DATE OF GMP INSPECTION: April 18-21, 2006

DATE OF NOTICE OF APPROVAL
TO APPLICANT:

II. INDICATIONS FOR USE:

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.

III. 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.**

IV. WARNINGS AND PRECAUTIONS:

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 Biohazardous Material. All technicians operating the CryoSeal FS System must be trained in the proper handling and disposal of blood by–products and biohazardous waste. Dispose of biohazardous materials in a biohazardous waste container in accordance with appropriate regulations.

The CryoSeal FS System is designed in accordance with Protection Class 1 (IEC). The chassis of the CryoSeal FS CS-1 is connected to the ground by a cable. Surfaces on the CS-1 that the operator may come in contact with are connected to the chassis by screw connections. For protection against electrical shock hazards, the System must be directly connected to a properly grounded electrical source approved by a qualified electrician. Contact ThermoGenesis Corp. for assistance with questions concerning the electrical connection for the system.

The CryoSeal FS System must not be used in the operating room.

V. DEVICE DESCRIPTION:

The CryoSeal FS System is a medical device that prepares the two components of fibrin sealant, cryoprecipitate and thrombin, from a unit of autologous plasma. The components of the system are the CS-1 instrument, the single-use sterile, pre-packaged CP-3 disposable, a pre-filled Thrombin Processing Chamber (TPC) Reagent syringe, disposable applicator components, a warming tray, and a harvest rack. These components are described below.

CS-1 Instrument

The CryoSeal FS System instrument (referred to as the CS-1) is a compact, upright floor-model device that semi-automatically produces cryoprecipitate and thrombin preparations from a unit of autologous plasma.

The CS-1 consists of the following subsystems: heat transfer plate, heat transfer plate rocking mechanism, refrigeration unit, heater mechanism, vacuum system, peristaltic pump, microprocessor control system, user interface display panel and operation buttons, Thrombin Processing Chamber (TPC) clips.

The CS-1 instrument requires the CP-3 plasma processing disposable to function.

CP-3 Disposable

The CP-3 Disposable is a single-use component that contains the cryoprecipitate chamber, the Thrombin Processing Chamber (TPC), transfer tubing, and a sterile syringe set collection and storage system.

Cryoprecipitate Chamber

The Cryoprecipitate Chamber consists of a clear, plastic container with a flat bottom and raised upper portion with a 0.2 micron sterile air vent to allow passage of the internal air displaced by incoming plasma and outgoing cryo-poor plasma.

Thrombin Processing Chamber (TPC)

The TPC consists of a tubular reaction chamber containing negatively charged ceramic beads and glass microspheres, a filter for removing gelled fibrin and other particulate matter from the final thrombin preparation, a 0.2 micron sterile air vent to allow passage of air needed to displace the thrombin preparation from the reaction chamber, and a syringe used to create suction or displacement needed to move plasma in and out of the reaction chamber.

The Collection and Storage System

The CP-3 utilizes four (4) pairs of physically connected 3 cc syringes as storage containers of the cryoprecipitate and thrombin. Within each pair of 3 cc syringes, one syringe contains cryoprecipitate solution and the other an equal volume of thrombin solution. Each pair of 3 cc syringes is enclosed in a single sterile overwrap. The four (4) pairs of syringes are filled sequentially to predetermined volumes. After filling, the individual overwraps are aseptically disconnected from the CP-3 by creating three (3) consecutive radio frequency (RF) seals in the adjacent tubing and breaking the center seal.

Transfer Tubing

The CP-3 contains standard medical grade transfer tubing. The transfer tubing contains a sterile docking segment for joining to the plasma bag by means of a sterile docking device.

Thrombin Processing Chamber Reagent

Thrombin Processing Chamber (TPC) Reagent is packaged in a pre-filled BD HyPak glass syringe. It comprises Ethanol, USP and Calcium Chloride, USP dissolved in Water-For-Injection, USP to final concentrations of 66.6% (v/v) and 25 millimolar, respectively. The TPC Reagent is terminally sterilized using steam sterilization, and then placed into an overwrap pouch to maintain its cleanliness.

Fibrin sealant (FS) Applicator System

The FS Applicator System consists of three components: a) a Spray Tip, b) a Line/Drop Tip, and c) a Handle. The Handle doses 200 μl of CryoSeal FS autologous fibrin sealant per trigger pull.

The Warming Tray

The FS Warming Tray is designed to hold assembled FS syringe sets and warm the fibrin sealant components to 34-37°C, prior to use.

The Harvest Rack
The Harvest Rack is an accessory on which the CP-3 is hung during harvest of the cryoprecipitate and thrombin. The Harvest Rack is a pole with a template for hanging and organizing the CP-3 disposable, allowing the use of both hands during the harvesting steps.

Source of Plasma

TO BE USED WITH AUTOLOGOUS PLASMA ONLY

Principles of Operation
The CryoSeal FS System prepares the fibrin sealant components, cryoprecipitate and thrombin, simultaneously from a unit of autologous plasma in approximately 60 minutes. The cryoprecipitate chamber harvests an average of 6 ml fibrinogen-rich cryoprecipitate and the TPC, in the presence of ceramic beads and borosilicate glass microspheres harvests an average of 8 ml thrombin containing solution. The CS-1 instrument provides step by step instructions guiding the user through the entire process of fibrin sealant component preparation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES:

There are a variety of medical devices and biologics indicated for use as adjuncts to hemostasis including absorbable gelatin powder and sponges, bovine gelatin matrix, bovine collagen sheets, oxidized cellulose sponges, topical bovine thrombin and fibrin sealants derived from pooled human plasma.

VII. MARKETING HISTORY:

The CryoSeal FS System has been sold since 1998. It is CE-marked and available for sale in the European Union as well as Argentina, Brazil, China, Colombia, Israel, Mexico, Russia, Saudi Arabia and Taiwan. The device has not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

VIII. 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 table contains a complete list of adverse events reported in greater than or equal to 1% of patients participating in the pivotal clinical trial for the CryoSeal FS System.

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%)
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%)

Adverse Event	Fibrin Sealant	Collagen Absorbable
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.

IX. SUMMARY OF PRECLINICAL STUDIES:

A pre-clinical study was performed to investigate time to hemostasis after application of fibrin sealant prepared using the CryoSeal FS System during pig liver resection surgery. The protocol was executed under GLP. Liver surgery was performed on 10 pigs. Time to hemostasis was determined for each surgery and a 90 minute post-operative follow-up examination was performed to confirm that no re-bleeding had occurred and that there was an absolute cessation of bleeding on the resected liver surface. Results revealed that the average time to hemostasis was 3.89 minutes with a standard deviation of 0.79 minutes, and the average total volume of fibrin sealant used per surgery was 7.54 ml with a standard deviation of 0.33 ml. All pigs survived the surgery and were alive at the 90 minute post-op follow-up exam exhibiting 100% cessation of bleeding at that time.

Biocompatibility

Compliant biocompatibility testing on the CP-3 plasma processing disposable, CryoSeal FS Applicator components, and the TPC Reagent was performed according to ANSI/AAMI/ISO 10993 including: Hemocompatibility/Hemolysis Test, Intracutaneous Reactivity Test, Cytotoxicity/MEM Elution Test, Genotoxicity (AMES), Maximization Sensitization Test, and Systemic Toxicity Test.

X. SUMMARY OF CLINICAL STUDIES:

PILOT STUDY

Study Objective

A safety pilot trial involving eight (8) study patients from one study center was conducted. These patients were treated with the autologous fibrin sealant prepared using the CryoSeal FS System to assess product safety, dosing, and technical aspects of fibrin sealant application.

Study Design

Eight (8) patients at ---------- scheduled to undergo hepatic resections for non-transplant and non-trauma surgeries were included in the clinical trial. Due to the small population, only summary statistics were presented. Two (2) patients involved in the study were female, and six (6) patients were male. The median age was 59.5 years old (range: 28 - 71 years old). ----------
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---------- None of the eight patients was diagnosed with cirrhosis of the liver.

Prior to surgery, seven (7) patients donated ------ of plasma by ----------. One patient donated ------- plasma by ---------- and ----------
----------. From the plasma, autologous fibrin sealant (FS) components were produced using the CryoSeal FS System. CryoSeal FS production was accomplished in about ---------. CryoSeal FS components were stored ----------
---------- awaiting surgery.

During surgery, the CryoSeal FS components ---------- the warming tray at 34-37^{o}C; ----------. The --------- component solutions were applied to transected liver surface with the CryoSeal FS dual syringe applicator that mixes cryoprecipitate and thrombin solutions *in situ* prior to application. Data recorded included ----------
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---------. Hemostasis data recorded included ----------

Study Results

Recovery data indicated there were no serious adverse events (SAE) or unanticipated adverse device events (UADE) reported for the eight patients. The two (2) adverse events observed after 30 days (abscess and hypophosphatemia) were found to be unrelated to CryoSeal FS product.

PIVOTAL 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. One hundred (100) patients were randomized to the study group: autologous fibrin sealant prepared using the CryoSeal FS System. Fifty three (53) patients were randomized to the control group: collagen absorbable hemostatic device, INSTAT (Ethicon, Inc.). Of the 153 patients, 118 were evaluated for effectiveness from which 77 patients were randomized to autologous fibrin sealant group and 41 patients were randomized to the control group. All 153 patients were evaluated for safety. Time to hemostasis at the surface of the incised liver after product application was measured and recorded. All study personnel were blinded to the treatment group until immediately prior to product application (T3). Each patient was monitored for 30 ± 3 days post-operatively.

Study Endpoints

The primary efficacy endpoint was time to hemostasis. Secondary efficacy endpoints were: (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.

See next page

Study Results

Primary Efficacy Endpoint

The median time to hemostasis for the CryoSeal FS group was 3.48 minutes compared to 6.67 minutes for the control group. The 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).

Time to Hemostasis
Intent-to-Treat Population

	Statistic	Fibrin Sealant (N=77)	Collagen Absorbable (N=41)	Difference (Fibrin Sealant– Collagen Absorbable) [95% C.I.]	p-value
Number of Patients Achieving Hemostasis	N (%)	77 (100%)	41 (100%)		
Time (Minutes) to Hemostasis for Patients Who Achieved Hemostasis	Mean	4.84	7.60	----------	< 0.001
	S.D.	-----	------		
	Median	3.48	6.67		
	Min – Max	----------	----------		

Secondary Efficacy Endpoints

Hemostasis within 10 minutes: 94.8% of patients in the fibrin sealant 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 the fibrin sealant group and the control group.

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 the fibrin sealant group and the control group.

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

Re-operation due to bleeding: The need for re-operation due to bleeding was not statistically different between groups, 2.6% in the fibrin sealant group compared to 0% in the control group (p=0.543). The need for re-operation was unrelated to the application of the fibrin sealant.

Conclusion

A statistically significant decrease in mean time to hemostasis was achieved after application of autologous fibrin sealant prepared using the CryoSeal FS System compared to INSTAT, collagen hemostatic device ($p<0.001$). The percentage of patients achieving hemostasis within 10 minutes was greater after using CryoSeal FS System produced autologous fibrin sealant (94.8%) vs. INSTAT (75.6%). However, post-operative transfusion requirements and need for re-operation due to bleeding were not different between the two study groups.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES:

The results of this clinical trial demonstrated that the autologous fibrin sealant prepared using the CryoSeal FS System was as safe, tolerable, and effective as collagen absorbable hemostatic device in this patient population and for this indication.

XII. CBER DECISION:

A GMP inspection was conducted of ThermoGenesis, Inc. facilities in Rancho Cordova, CA from April 18-21, 2006 and they were found to be in compliance with the device Quality System Regulations.

CBER issued an approval order on

XIII. APPROVAL SPECIFICATIONS:

Directions for Use: See Package Insert

Hazards to Health from use of the device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the Package Insert

Post-approval Requirements and Restriction: See Approval Order