CoStasis™ Surgical Hemostat
Instructions for Use

DO NOT INJECT.
CoStasis® Surgical Hemostat ("CoStasis") must not be injected into blood vessels.

Device Description and Action:

CoStasis includes:

1. A CoStasis syringe containing a suspension of 20 mg/ml bovine collagen and at least 300 U/ml bovine thrombin in a 40 mM $CaCl_2$ buffer.

2. A Delivery System containing accessories used for joining the CoStasis syringe to the autologous plasma syringe, and for mixing and delivering the fluids.

3. A Transfer Syringe used to receive the patient's plasma and provide a means for placing the plasma into the sterile operating field.

CoStasis is used in conjunction with the patient's own plasma. A product called CellPaker® Plasma Collection Device is supplied separately and is used for obtaining the patient's plasma.

The bovine thrombin in CoStasis converts autologous plasma fibrinogen to fibrin, which, in the presence of collagen, forms a collagen/fibrin gel matrix which adheres to the bleeding site. CoStasis is biocompatible, non-pyrogenic, and resorbed within 30 days and is intended to be left *in situ*.

Indications:

CoStasis 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 CoStasis into blood vessels or allow it to enter blood vessels. Extensive intravascular clotting and even death may result.

- Do not use CoStasis in patients with known allergies to materials of bovine origin.

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

Warnings:

- CoStasis is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis.

- CoStasis should not be used in the presence of infection. CoStasis should be used with caution in contaminated areas of the body. If signs of infection or abscess develop where CoStasis has been applied, reoperation may be necessary in order to remove the infected material and allow drainage.

- Do not use CoStasis in instances of profuse arterial bleeding. It should not be used where blood or other fluids have pooled or in cases where the point of hemorrhage is submerged.

- The safety and effectiveness of CoStasis for use in neurosurgical, ophthalmic, and urological procedures have not been established.

- CoStasis should not be used for controlling post-partum bleeding of menorrhagia.

- The safety and effectiveness of CoStasis have 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 increase 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 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:

- CoStasis is supplied as a sterile product for single use only. Do not resterilize.
- Excess CoStasis 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.
- As with other hemostatic agents, do not aspirate CoStasis 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.
- CoStasis 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.
- CoStasis should not be used for the primary treatment of coagulation disorders.
- The safety and effectiveness of the combined use of CoStasis with antibiotic solutions or powders have not been established.

See Precautions in the Package Insert for Thrombin-JMI® enclosed in the CoStasis package.

Adverse Events:

In a randomized prospective, concurrently controlled clinical trial, 318 patients were treated with CoStasis or the Control (a collagen absorbable hemostat for the non-cardiac procedures, and other conventional methods selected by the surgeon for cardiac procedures). The most common adverse events recorded during and after the application of the hemostatic agents were fever, pain, nausea, and atelectasis. The following is a complete list of adverse events reported in greater than 5% of CoStasis treated patients that were observed in the clinical trial. The corresponding adverse events for the Control group are listed for comparison. None of the adverse events listed in the table were determined to be attributed to CoStasis.

Adverse Events Reported in Greater than 5% of Patients in CoStasis Clinical Trial Patients		
Adverse Event	CoStasis	Control* (absorbable collagen hemostat)
Fever	51 (30.4%)	41 (27.3%)
Pain	38 (22.6%)	33 (22.0%)
Nausea	34 (20.2%)	29 (19.3%)
Atelectasis	32 (19.0%)	27 (18.0%)
Pleural Effusion	24 (14.3%)	28 (18.7%)
Anemia	23 (13.7%)	27 (18.0%)
Peripheral Edema	19 (11.3%)	11 (7.3%)
Tachycardia	16 (9.5%)	20 (13.3%)
Constipation	14 (8.3%)	9 (6.0%)
Rash	14 (8.3%)	15 (10.0%)
Infection	13 (7.7%)	13 (8.7%)
Abnormal Healing	12 (7.1%)	12 (8.0%)
Abdominal Pain	11 (6.5%)	15 (10.0%)
Edema	11 (6.5%)	7 (4.7%)
Lung Disorder	11 (6.5%)	11 (7.3%)
Pericarditis	10 (6.0%)	13 (8.7%)
Nausea/Vomiting	10 (6.0%)	8 (5.3%)
Lung Edema	9 (5.4%)	9 (6.0%)
Pneumonia	9 (5.4%)	9 (6.0%)
Pruritis	9 (5.4%)	12 (8.0%)

*For the cardiac group, the control was selected by the surgeon, based on his/her conventional methods, including absorbable collagen hemostats, surgical tamponade, electrocautery with or without tamponade, gelatin sponge with thrombin, or no treatment.

Other adverse events observed in less than 5% of the CoStasis treated clinical trial patients were bleeding, hypertension, hypotension, dyspnea, urinary tract infection, back pain, apnea, abscess, allergic reaction, death, chest pain, ecchymosis, hypokalemia, confusion, ileus, pharyngitis, ascites, asthenia, headache, atrial fibrillation, hypervolemia, dizziness, insomnia, paresthesia, increased coughing, oliguria, sepsis, arrhythmia, diarrhea, jaundice, hypomagnesemia, bone pain, anxiety, respiratory disorder, skin ulcer, hematuria, abnormal kidney function, fibrotic surgical wound, necrosis, pain at injection site, angina pectoris, heart arrest, heart failure, ventricular tachycardia, gastritis, GI disorder, melena, vomiting, leukocytosis, leukopenia, acidosis, bilirubinemia, hyperglycemia, hyponatremia, agitation, depression, hallucination, abnormal thinking, pneumothorax, sweating, kidney failure, breast pain, abdominal enlargement, cellulitis, chills, edema at injection site, hernia, anemia, cardiovascular disorder, extrasystoles, shock, syncope, superior ventricular tachycardia, anorexia, dyspepsia, GI bleeding, rectal bleeding, abnormal liver function, oral monilia, increased coagulation time, thrombocytopenia, increased creatinine, cyanosis, hypoglycemia, hypophosphatemia, joint disorder, myasthenia, abnormal dreams, stupor, asthma, voice alteration, skin disorder, abnormal urination, vaginitis, asthesia, granuloma, hypothermia, injection site reaction, injury accident, neck rigidity, necrosis at injection site, overdose, sarcoma, seroma, thirst, vascular anomaly, sinus bradycardia, bundle branch block, cardiomegaly, pericardial effusion, ventricular extrasystoles, myocardial infarction, deep thrombophlebosis, thrombosis, thrombophlebosis, peripheral vascular disorder, varicose vein, anastomosis leak, liver carcinoma, colitis, eructation, dysphagia, tongue edema, fecal incontinence, liver failure, stomatitis, tooth disorder, agranulocytosis, hypovolemia, seroma, alkalosis, avitaminosis, dehydration, general edema, gout, hypocalcemia,

arthrosis, myalgia, general spasm, aphasia, convulsions, hemiplegia, hypertonia, movement disorder, neuropathy, bronchiectasis, pulmonary embolism, emphysema, hemoptysis, hyperventillation, hypoxemia, hypoxia, infection, lung function decrease, rhinitis, vesiculobullous rash, bone pain, eye pain, breast carcinoma, epididymitis, impotence, urinary incontinence, metrorrhagia, nephrosis, urethral pain, testis disorder, urinary retention.

One adverse event was deemed by the surgeon to be related to the use of CoStasis: blocked inguinal drainage tube reported on day 11 post surgery. No other adverse events were deemed by the surgeon to be related to the use of CoStasis.

Adverse Events That Have Been Attributed to Other Absorbable Hemostatic Agents:

- Absorbable 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 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 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 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 hemostatic agents were used in severed tendon repair.

- Toxic shock syndrome was reported in association with the use of absorbable hemostatic agents 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 the Adverse Reactions Section in the Package Insert for Thrombin-JMI® enclosed in the CoStasis package.

Clinical Studies:

Study Design and Objectives: A prospective, randomized, controlled, multi-center, multi-specialty study was conducted. Three hundred and eighteen (318) patients were enrolled at 10 centers. The objective of the study was to evaluate the safety and effectiveness of CoStasis™ Surgical Hemostat versus an absorbable collagen hemostatic sponge in patients undergoing general, hepatic, and orthopedic surgeries, or versus conventional methods in patients undergoing cardiac surgery, in controlling intraoperative bleeding. This study was designed to evaluate whether the CoStasis success rate was equivalent to the success rate for the control.

Of the 318 patients enrolled in this study, 167 patients were treated with CoStasis (79 patients were in the General Surgery Group, 39 patients were in the Hepatic Surgery Group, 12 patients were in the Iliac Crest Group, and 37 patients were in the Cardiac group). For the Cardiac Group, enrolled patients were treated in at least one study site (anastomotic, sternal edge, or capillary bed) and were allowed to be treated at some or all of the three study sites.

Primary Endpoint: The primary effectiveness outcome parameter measured was the cessation of bleeding at a treatment site within the allotted time of 10 minutes (3 minutes for cardiac surgery). The study data for the number of treatment sites achieving complete hemostasis are shown in the tables below.

Treatment Sites Achieving Complete Hemostasis Within 10 Minutes
Intent-to-Treat Sites
(Success/Total)

Surgical Group	CoStasis	Control
All Treated Sites (non-cardiac group)	97% (126/130)	66% (75/114)
General	97% (77/79)	67% (50/75)
Hepatic	100% (39/39)	69% (20/29)
Iliac Crest	83% (10/12)	50% (5/10)

Treatment Sites Achieving Complete Hemostasis Within 3 Minutes
Intent-to-Treat Sites
(Success/Total)

Cardiac Group	CoStasis	Control*
All Treated Sites	93% (74/80)	55% (46/84)
Anastomotic	97% (28/29)	59% (17/29)
Sternal Edge	83% (25/30)	44% (15/34)
Capillary Bed	100% (21/21)	67% (14/21)

*For the cardiac group, the control was selected by the surgeon, based on his/her conventional methods, including absorbable collagen hemostats, surgical tamponade, electrocautery with or without tamponade, gelatin sponge with thrombin, or no treatment.

Cumulative Percent of Treatment Sites with Complete Hemostasis Over 10 Minutes
Intent-to-Treat Sites for General, Hepatic, and Iliac Crest Groups
(Success/Total)

Time Interval	CoStasis	Control
0 – 1 minute	37% (48/130)	4% (5/114)
1 – 2 minutes	60% (78/130)	17% (19/114)
2 – 3 minutes	75% (97/130)	27% (31/114)
3 – 6 minutes	94% (122/130)	50% (57/114)
6 – 10 minutes	97% (126/130)	66% (75/114)

Cumulative Percent of Treatment Sites with Complete Hemostasis Over 3 Minutes
Intent-to-Treat Sites for Cardiac Group
(Success/Total)

Time Interval	CoStasis	Control
0 – 1 minute	51% (41/80)	2% (2/84)
1 – 2 minutes	75% (60/80)	20% (17/84)
2 – 3 minutes	93% (74/80)	55% (46/84)

CoStasis and control were shown to be equivalent using the Blackwelder and Chang test, using a δ (clinically significant difference) of 0.25 ($p < 0.01$). For treatment sites achieving complete hemostasis, the difference between CoStasis and control was also shown to be statistically significant using the Fisher's Exact test ($p < 0.05$), except for the Iliac Crest Group ($p = 0.17$).

Secondary Endpoint: A secondary endpoint was time to achieve complete hemostasis. The study data for times to achieve complete hemostasis are shown in the tables below.

Times to Achieve Complete Hemostasis
General, Hepatic and Iliac Crest Groups
Median ± 1 standard error

Surgical Group	CoStasis (seconds)	Control (seconds)
All Patients	90 ± 20	347 ± 27
General	65 ± 13	345 ± 63
Hepatic	150 ± 19	360 ± 52
Iliac Crest	90 ± 35	347 ± 343

Times to Achieve Complete Hemostasis
Cardiac Group
Median ± 1 standard error

Treatment Site	CoStasis (seconds)	Control (seconds)
All Treatment Sites	55 ± 4	180 ± 6
Sternal Edge	68 ± 33	> 180
Anastomosis	62 ± 12	180 ± 53
Capillary Bed	50 ± 5	180 ± 19

The times to achieve complete hemostasis for all study groups were statistically different using the Breslow-Gehan-Wilcoxon test ($p < 0.05$).

Immunology Results: Antibody data were available for 92 patients in the CoStasis group and 84 patients in the Control group, with both pre-treatment and 8-week follow-up serum samples. Twenty-seven (27) patients (29%) in the CoStasis group and 10 patients (12%) in the Control group developed antibodies to bovine Thrombin ($p = 0.0053$, Fisher's Exact Chi-square). One (1) patient (1%) in the CoStasis group and 1 patient (1%) in the Control group developed antibodies to bovine Factor V_a ($p = 0.99$, Fisher's Exact Chi-square).

Cross-reactivity to human thrombin was observed in 8 patients in the CoStasis group, and 1 patient in the Control group. There was no statistically significant difference between the two groups ($p = 0.21$, Fisher's Exact Chi-square). There was no cross-reactivity to

human Factor V_a, in either the CoStasis or Control groups. All patients who tested positive for antibodies to human thrombin had Prothrombin times within normal limits (< 15 seconds), except one CoStasis patient whose Prothrombin time was 23.7 seconds pre-surgery and 16.6 seconds post-surgery. This patient had a history of metastatic colon cancer to the liver and underwent a right hepatic lobectomy.

How Supplied:

CoStasis Surgical Hemostat is supplied as a single use only 5-ml treatment syringe, which is packaged with sterile delivery components and a sterile transfer syringe. CoStasis is combined with an equal volume of patient plasma.

Sterile Delivery System and sterile Transfer Syringe are included. Sterile CellPaker available separately in single or multiple unit boxes.

Do not use if package is damaged or if syringe caps are dislodged or missing.

The CellPaker Plasma Collection Device (CellPaker) is a single use sterile device used to draw patient blood, be placed into a centrifuge and obtain patient plasma. The device contains sodium citrate as an anticoagulant. The CellPaker Plasma Collection Device is available in multiple unit boxes.

Do not use if CellPaker cap is dislodged or missing.

Storage Conditions:

Store CoStasis® Surgical Hemostat at 2 - 8 °C. **Do not freeze.**
Store the CellPaker Plasma Collection Device at room temperature.

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

See Attached Directions for Use

Manufacturer:

Cohesion Technologies, Inc.
2500 Faber Place
Palo Alto, CA 94303 U.S.A.

CellPaker® Plasma Collection Device
Directions for Use

Description

The CellPaker Plasma Collection Device (CellPaker) is a single use sterile device used to draw patient blood, be placed into a centrifuge and obtain patient plasma. The device contains sodium citrate as an anticoagulant. The device is intended to be used with CoStasis™ Surgical Hemostat.

Label CellPaker with patient identification. Remove cap and expel air from CellPaker by pushing plunger rod up.

Connect CellPaker to intravenous or arterial line. Pull back on plunger rod to fill CellPaker with blood to capacity (~ 12 ml). It is preferred, but not required, that this step be done before the patient is administered heparin.

Replace CellPaker cap. Mix contents.

Unscrew and discard plunger rod from CellPaker.

Place CellPaker in centrifuge; capped luer tip up. Balance centrifuge by placing a weight or a second full CellPaker in opposite chamber. Close and lock centrifuge lid. Set the speed and the timer and start the centrifuge. Allow the centrifuge to come to a complete stop before removing the CellPaker.

Refer to CoStasis™ Surgical Hemostat Instructions for Use

How Supplied

The CellPaker Plasma Collection Device containing sodium citrate is available in single or multiple unit boxes.

Do not use if CellPaker cap is dislodged or missing.

Storage Conditions

Store at room temperature

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

Manufacturer:
Cohesion Technologies, Inc.
2500 Faber Place
Palo Alto, CA 94303 U.S.A.

Please note: For the Directions or Use (DFUs) supplied, the pictures have been removed. The pictures will be used in the actual package labels.

Directions for Use

Label CellPaker with patient identification. Remove cap and expel air from CellPaker by pushing plunger rod up.

Connect CellPaker to intravenous or arterial line. Pull back on plunger rod to fill CellPaker with blood to capacity. It is preferred, but not required, that this step be done before the patient is administered heparin.

Replace CellPaker cap. Mix contents.

Unscrew and discard plunger rod from CellPaker.

Place CellPaker in centrifuge; capped Luer tip up. Balance centrifuge by placing a weight or a second full CellPaker in opposite chamber. Close and lock centrifuge lid. Set the speed and timer and start the centrifuge. Allow the centrifuge to come to a complete stop before removing the CellPaker.

How to Assemble CoStasis® Surgical Hemostat

1. **Remove CellPaker from centrifuge and hold in a vertical position with the Luer tip up. Remove cap from Luer tip.**

2. **Connect Cell Paker to Transfer Syringe.**

   Remove and discard transfer syringe Luer cap. Transfer syringe tip is sterile. Attach transfer syringe to CellPaker.

3. **Transfer Plasma from CellPaker to Transfer Syringe.**

   Turn red outer sleeve of CellPaker to transfer plasma to syringe. The volume of plasma transferred should be equal to the volume of the CoStasis syringe being used.

4. **Place Plasma Containing Transfer Syringe into Sterile Field.**

   The transfer syringe containing plasma is sterile. Circulating nurse peels open transfer syringe pouch. Scrub nurse unscrews and removes plasma syringe and places into sterile field.

5. **Place the Sterile CoStasis Syringe into Sterile Field.**

   The CoStasis suspension syringe is sterile. Circulating nurse peels open the CoStasis syringe pouch. Scrub nurse unscrews and removes the CoStasis syringe.

6. **Expel Air from CoStasis and Plasma Syringes.**

7. **Assemble Syringes with Delivery System.**

   It is important to attach the cannula or sprayhead last.

   a. Attach Luer ends of CoStasis and plasma syringes to joiner.
   b. Align ends of plunger rods until even. Expel syringe contents, if necessary.
   c. Slide syringe clip over the ends of plunger rods.
   d. Slide support over assembled device until firmly seated.

8. **Attach Spray Head or Cannula, According to the Surgeon's Preference.**

The CoStasis™ Surgical Hemostat is now ready for use.

How to Apply CoStasis to the Bleeding Site

1. Discontinue all blood recovery and cell-saving devices, as appropriate. Blot surface dry.

2. Apply product as a thin, uniform coating and overlap the edges to ensure complete coverage. *Avoid disrupting the gel.*

3. If discrete bleeding is observed, additional CoStasis may be applied by underlying the formed gel with the tip of the cannula and delivering the material directly to the site.

4. If bleeding continues, remove the first application as completely as possible, blot, and reapply CoStasis.