TISSEEL
[Fibrin Sealant]

do you really know it

For Topical Use Only

BioSurgery-Advancing Surgery, Enhancing Life

Baxter

Evolution and Improvement

1972

Dr. Helene Matras

Reintroduction of modern tissue sealants by Helen Matras who successfully employed fibrin sealant for reuniting severed nerves in an animal model.[6,7]

image From Redl.[9] Used with permission.

1980

A special heating and stirring device, FIBRINOTHERM, is developed to dissolve lyophilized TISSEEL.[9]

1998

Fibrin sealant approved in the United States following TISSEEL clinical study led by Dr. John Rousou.[10]

Dr. John Rousou

2007

For Topical Use Only

Introduction of TISSEEL VH SD (frozen).[5]

1978

TISSEEL VH (lyophilized) introduced.[8,9]

1987

For Topical Use Only

A dual-syringe, deep frozen system for TISSEEL VH is introduced.[9]

2005,2006

The EASYSPRAY application system was introduced in 2005 and the DUPLOSPRAY system was introduced in 2006.[3]

2012

Introduction of TISSEEL VH SD (frozen) with synthetic aprotinin.[3]

What Makes TISSEEL Fibrin Sealant Different

The Only "4 in 1" Fibrin Sealant[1]

- Hemostasis
- Sealing
- Adherence
- Healing

Unique Formulation

- Fibrinogen content determines clot strength[7]
- Lower thrombin supports adhesion and spreading of NHEKs[12]
- Aprotinin promotes clot stabilization[2]

Component	TISSEEL[2]	EVICEL[11]
Fibrinogen	67-106 mg/mL	50-90 mg/mL
Thrombin	400-625 IU/mL	800–1,200 IU/mL
Aprotinin	2250-3750 KU/mL	---

Benefits of High Fibrinogen Concentration

- Fibrinogen concentration is directly related to:
  - Elasticity of the fibrin clot[9]
  - Increased tensile strength[7]
  - Increased adhesive strength[7]
- The TISSEEL fibrin clot contains:
  - 30 times the fibrinogen concentration in blood[20]
  - 5 times the strength of a normal, healthy clot[21]

Image from Redl[9]. Used with permission.

The physiologic fibrin clot formed by TISSEEL Fibrin Sealant has a high elasticity.[9]

Benefits of Low Thrombin Concentration

- Normal human epidermal keratinocytes (NHEK) play a key role in wound healing of the skin as they re-epithelialize the wound area[12]
- A lower thrombin concentration supports adhesion and spreading of NHEK *in vitro*[12]
- A lower thrombin concentration provides a more uniformly polymerized, stronger adhesive bond[13]

Morphology of NHEK on fibrin clots prepared with low, medium, and high concentrated thrombin solutions. Cells were seeded on top of fibrin clots with different thrombin contents: 505 IU mL (left); 820 IU mL (right) were incubated for 24 hours (top) or 48 hours (bottom). Cells were stained to visualize cell nuclei (blue stain).[12]

Striking differences in cell morphology were observed between fibrin clots made with low, medium, and high concentrated thrombin solutions. With increasing thrombin concentration cell morphology became more and more deteriorated.[12]

Image from Gugerall et al.[12] Used with permission.

What Makes TISSEEL Fibrin Sealant Different

In Vitro Comparison of Clot Lysis Under Highly Fibrinolytic Conditions[14]

Image adapted from Hedrich et al.[14] Used with permission.

In highly fibrinolytic conditions, the TISSEEL clot is more stable than a clot prepared from plasminogen-depleted and aprotinin-free fibrin (EVICEL). When EVICEL was supplemented with aprotinin, it had a stabilizing effect on the clot.[14]

Statistically significant difference $p < 0.001$

TISSEEL

EVICEL

Images from Hedrich et al.[14] Used with permission.

Ultrastructure of TISSEEL (top) and EVICEL (bottom). TISSEEL clots are formed of thick fibrin fibers. EVICEL is formed of thin fibrin fibers with a dense, less homogenous structure.[14]

Key Study Conclusions[14]

- When comparing TISSEEL and EVICEL *in vitro*, there were differences in ultrastructure and alpha-chain cross-linking rates as well as the rate of fibrinolysis which may explain the significantly enhanced sealing efficacy of TISSEEL *in vivo* (in an animal model)
- Total clot lysis occurred within two days in the EVICEL clots and five days in the TISSEEL clots
- Interestingly, when aprotinin was added to EVICEL it had a stabilizing effect on the clots; time to achieve clot lysis was prolonged from 2 days to 8 days
- There was a statistically significant higher leakage pressure with pooled lots of TISSEEL than with pooled lots of EVICEL (two-sided $p < 0.0001$)
- In Hickerson et al,[15] the authors reported higher tensile strength and higher levels of factor XIII in EVICEL; investigations in this study contradict both of these findings

> *TISSEEL demonstrated statistically significant enhanced efficacy as compared to EVICEL.*[14]

TISSEEL Fibrin Sealant vs. EVICEL

Ease of Use

- Unlike EVICEL, after thawing TISSEEL (frozen) is ready-to-use with no additional preparation required[2,16]

TISSEEL*[2]	Thawing Time*	Prep. Personnel	EVICEL[16]	Preparation Time	Prep. Personnel
2 mL	5 minutes	Scrub nurse	1 mL	10 minutes + prep. time	Scrub & circulating nurse
4 mL	5 minutes	Scrub nurse	2 mL	10 minutes + prep. time	Scrub & circulating nurse
10 mL	12 minutes	Scrub nurse	5 mL	10 minutes + prep. time	Scrub & circulating nurse

*TISSEEL Frozen: quick thawing performed by immersion in a sterile water bath. Maintain product at 33-37°C until use.[2]

Coverage and Application - when applied using a spray device

Total Volume	TISSEEL[2]	EVICEL[16]
2 mL	100 cm^2	20 cm^2
4 mL	200 cm^2	40 cm^2
10 mL	500 cm^2	100 cm^2

2mL TISSEEL when dripped cover 10cm^2

TISSEEL provides 5x more coverage

TISSEEL (frozen) is ready-to-use[2]

For Topical Use Only

Easy as 1-2-3

For Topical Use Only

TISSEEL Fibrin Sealant vs. TACHOSIL

Coverage and Application - when applied using a spray device

- Unlike TACHOSIL, TISSEEL can be sprayed and used with a wide variety of application devices, thus it is ideal for minimally-invasive as well as open procedures[1,2,17,18]
- TACHOSIL is only provided as a sponge that may stick to instruments or gloves[19]

Size	TISSEEL[1,2]
2 mL	100 cm^2
4 mL	200 cm^2
10 mL	500 cm^2
10 mL	500 cm^2

2mL TISSEEL when dripped cover 10cm^2

Size	TACHOSIL[19]
3.0 cm x 2.5 cm (1 sponge)	7.5 cm^2
3.0 cm x 2.5 cm (5 sponges)	37.5 cm^2
9.5 cm x 4.8 cm (1 sponge)	45.6 cm^2
4.8 cm x 4.8 cm (2 sponges)	46.1 cm^2

TISSEEL provides (at least) 5x more coverage

Wide Variety of Applicators Available[2,17,18]

Spray application precaution: Any application of pressurized gas may be associated with a potential risk of air embolism, tissue rupture or gas entrapment with compression, which may be life threatening. Be sure to take appropriate measures to address these risks by observing the recommended minimum spraying distance and the maximum pressure provided in the appropriate spray set instructions for use.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TISSEEL safely and effectively. See full prescribing information for TISSEEL.

TISSEEL [Fibrin Sealant]
For Topical Use Only
Frozen solution and lyophilized powder for solution for topical application
Initial U.S. Approval: 1998

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) xx/2013

----------INDICATIONS AND USAGE----------

Hemostasis: TISSEEL is a fibrin sealant indicated for use as an adjunct to hemostasis in adult and pediatric patients (>1 month of age) undergoing surgery when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. TISSEEL is effective in heparinized patients.(1.1)

Sealing: TISSEEL is a fibrin sealant indicated as an adjunct to standard surgical techniques (such as suture and ligature) to prevent leakage from colonic anastomoses following the reversal of temporary colostomies (1.2)

----------DOSAGE AND ADMINISTRATION----------

For Topical Use Only. Do Not Inject (2)

- Apply TISSEEL as a thin layer by dripping or spraying using cannula or spray set (2.3, 5.2)
- Ensure that the amount of TISSEEL to be applied is sufficient to entirely cover the intended application area (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

TISSEEL Kit (Freeze-Dried) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with and without the DUPLOJECT System (3)

TISSEEL Pre-filled Syringe (Frozen) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with the DUO Set (3)

----------CONTRAINDICATIONS----------

- Do not inject directly into the circulatory system or into highly vascularized tissue (4.1, 5.3)
- Do not use in individuals with a known hypersensitivity to aprotinin (4.2, 5.1, 6)
- Do not use for the treatment of severe or brisk arterial or venous bleeding (4.3)

----------WARNINGS AND PRECAUTIONS----------

- TISSEEL contains aprotinin, a protein known to be associated with anaphylactic reactions (4.2, 5.1, 6)
- Air or gas embolism has occurred when fibrin sealant was administered using pressurized gas. This can occur if a spray device is used at higher than recommended pressures and in close proximity to the surface of the tissue (5.2)
- TISSEEL is denatured when exposing to solutions containing alcohol, iodine or heavy metals (5.2)
- Apply only as a thin layer as excess clot thickness can negatively interfere with wound healing (2, 5.2)
- Exercise caution to minimize the risk of intravascular application when using TISSEEL in surgery (4.1, 5.3, 6.2)
- Safety has not been evaluated in neurosurgical procedures (5.4)
- TISSEEL is made from pooled human plasma which can contain infectious agents (5.5)

----------ADVERSE REACTIONS----------

Hypersensitivity or allergic/anaphylactoid reactions have occurred (6)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Oxidized cellulose-containing preparations can reduce the efficacy of TISSEEL and should not be used as carrier materials (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: No human or animal data. Use only if clearly needed (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: xx/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hemostasis: TISSEEL is a fibrin sealant indicated for use as an adjunct to hemostasis in adult and pediatric patients (>1 month of age) undergoing surgery when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. TISSEEL is effective in heparinized patients.

1.2 Sealing: TISSEEL is a fibrin sealant indicated as an adjunct to standard surgical techniques (such as suture and ligature) to prevent leakage from colonic anastomoses following the reversal of temporary colostomies.

2 DOSAGE AND ADMINISTRATION

FOR TOPICAL USE ONLY – DO NOT INJECT

Vials and pre-filled syringes are for single use only. Discard any unused product.

2.1 Preparation of TISSEEL Kit (Freeze-Dried)

DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C
DO NOT MICROWAVE
DO NOT REFRIGERATE OR FREEZE AFTER RECONSTITUTION

Do not use iodine or heavy metal containing preparations such as betadine for disinfection of vial stoppers.
Allow alcohol-based disinfectants to evaporate before puncturing stopper.

Use separate syringes and transfer devices for reconstituting Sealer Protein and Thrombin solutions and for application to prevent clotting.
The product must be used within 4 hours after reconstitution.

Freeze-dried Sealer Protein Concentrate and Thrombin are reconstituted in Fibrinolysis Inhibitor Solution and Calcium Chloride Solution, respectively. The Sealer Protein Solution and Thrombin Solution are then combined using the DUPLOJECT Preparation and Application System, or an equivalent delivery device cleared by FDA for use with TISSEEL, to form the Fibrin Sealant.

Prewarming TISSEEL Kit with FIBRINOTHERM

See FIBRINOTHERM manual for complete operating instructions. If a FIBRINOTHERM device is not available, contact Baxter (1-800-423-2090) for assistance.

1. Place all four vials from the TISSEEL Kit into the prewarmed wells of the FIBRINOTHERM, using the appropriately sized adapter ring(s), and allow the vials to warm for up to 5 minutes (room temperature product will take less time).

Preparation of Sealer Protein Solution with FIBRINOTHERM

1. Remove the caps from the Sealer Protein Concentrate and the Fibrinolysis Inhibitor Solution vials.
2. Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein Concentrate using the sterile reconstitution components (see directions provided with the device system for specific reconstitution instructions). Gently swirl the vial to ensure that the product is completely soaked.
3. Place the vial into the largest opening of the FIBRINOTHERM device with the appropriate adaptor. Switch on the stirrer and allow the vial contents to stir until all Sealer Protein Concentrate is dissolved. Reconstitution is complete when no undissolved particles are visible.

Notes:

- If the Sealer Protein Concentrate has not fully dissolved within 20 minutes discard the vial and prepare a fresh kit.
- Keep the Sealer Protein Solution at 37°C without stirring. Stir shortly before drawing up the solution to ensure homogeneity.

Preparation of Thrombin Solution with FIBRINOTHERM

To reconstitute the Thrombin (Human) with the Calcium Chloride Solution; follow steps 1-3 under **Preparation of Sealer Protein with FIBRINOTHERM** utilizing the Thrombin and Calcium Chloride vials.

Transferring to the Sterile Field

For transfer of the Sealer Protein and Thrombin Solutions to the sterile field, the circulating nurse should disinfect the tops of the vials with a germicidal solution and allow to dry. The scrub nurse should withdraw the sterile solutions while the circulating nurse holds the non-sterile vials. Slowly withdraw the solution, by firm constant aspiration, to reduce the risk of large air bubbles.

2.2 Preparation of TISSEEL Pre-Filled Syringe (Frozen)

DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C
DO NOT MICROWAVE
DO NOT REFRIGERATE OR RE-FREEZE

Do not use TISSEEL (frozen) until it is completely thawed and warmed (liquid consistency) to 33-37°C.
Do not remove the protective syringe cap until use.

Sterile Water Bath (Quick Thawing): Transfer inner pouch to the sterile field, remove pre-filled syringe from inner pouch and place directly into sterile water bath ensuring the syringe is completely immersed in the water. Maintain the product at 33-37°C until use. If the package is opened or warmed to 33-37°C, it must be used within 4 hours.

Non-Sterile Water Bath: Maintain the pre-filled syringe in pouches and place into a water bath outside the sterile field ensuring the pouches remain submerged. Remove from the water bath after thawing and warming, dry the external pouch and transfer inner pouch with pre-filled syringe onto the sterile field. Maintain the product at 33-37°C until use. If the package is opened or warmed to 33-37°C, it must be used within 4 hours.

Incubator: Maintain the pre-filled syringe in pouches and place into an incubator. Remove from the incubator after thawing and warming. Transfer inner pouch with pre-filled syringe onto the sterile field. Maintain the product at 33-37°C until use. If the package is opened or warmed to 33-37°C, it must be used within 4 hours.

Table 1: Approximate Water Bath or Incubator Thawing and Warming Times

Pack Size	Sterile Water Bath (Pouches Removed) 33 - 37°C	Non-Sterile Water Bath (In Pouches) 33 - 37°C	Incubator (In Pouches) 33 - 37°C
2 mL	5 minutes	30 minutes	40 minutes
4 mL	5 minutes	40 minutes	85 minutes
10 mL	12 minutes	80 minutes	105 minutes

Room Temperature Thawing: Unopened pouches can be stored for up to 48 hours at room temperature (15-25°C). Before use, warm the product to 33-37°C and apply immediately. The total thawing and warming time cannot exceed 48 hours.

Table 2: Approximate Room Temperature Thawing Times

Pack Size	Room Temperature (In Pouches) 15 – 25°C
2 mL	60 minutes
4 mL	110 minutes
10 mL	160 minutes

Table 3: Approximate Water Bath or Incubator Warming Times for Thawed Product

Pack Size	Sterile Water Bath (Pouches Removed) 33 – 37°C	Non-Sterile Water Bath (In Pouches) 33 – 37°C	Incubator (In Pouches) 33 – 37°C
2 mL	2 minutes	16 minutes	20 minutes
4 mL	2 minutes	21 minutes	43 minutes
10 mL	6 minutes	43 minutes	52 minutes

2.3 Method of Application

Dry the site of application as much as possible.

Apply TISSEEL as a thin layer by dripping or spraying using a cannula or spray set. The treating physician will determine the amount of TISSEEL to be applied based on the surface to be covered. Ensure that the amount applied is sufficient to entirely cover the intended application area. The approximate surface areas covered by each package size of TISSEEL are listed in Table 4:

Table 4: Surface Area Coverage

Required package size of TISSEEL	Maximum coverage using spray	Maximum coverage using cannula
2 mL	100 cm^2	8 cm^2
4 mL	200 cm^2	16 cm^2
10 mL	500 cm^2	40 cm^2

Avoid application beyond the intended area. Allow at least 2 minutes after application to achieve sufficient polymerization. If repeat application is needed, dry the site as much as possible before reapplying. Reapply after removing residues from the prior application or before polymerization takes place since TISSEEL may not adhere firmly to a polymerized layer.

In cases where very small volumes (1-2 drops) are required, expel and discard the first several drops from the application cannula immediately before application to ensure administration of adequately mixed TISSEEL.

Exercise caution when applying TISSEEL using pressurized gas (*see Warnings and Precautions (5.2)).*

Record the product name, batch number and patient information for traceability purposes.

TISSEEL Kit (Freeze-Dried)

Apply TISSEEL using the DUPLOJECT Fibrin Sealant Preparation and Application System or an equivalent delivery device (including open and minimally invasive spray devices) cleared by FDA for use with TISSEEL. Specific instructions for the use of TISSEEL in conjunction with each cleared delivery device are provided with the device.

TISSEEL Pre-filled Syringe (Frozen)

Apply pre-filled TISSEEL using the DUO Set accessory devices provided with the product or an equivalent delivery device (including open and minimally invasive spray devices) cleared by FDA for use with TISSEEL.

DUO Set Instructions (see Figure 1 below):

1. Insert plunger into syringe barrel.
2. Firmly connect the two syringe nozzles to the joining piece (Y connector) and secure it by fastening the tether strap to the syringe.
3. Fit an application cannula to the joining piece. Apply by depressing plunger.

Note: Interruption of TISSEEL application causes clogging in the cannula. Replace the cannula immediately prior to resuming application. If the opening of the joining piece (Y connector) facing the cannula is clogged, use the spare joining piece provided in the package.

Figure 1
DUO SET

3 DOSAGE FORMS AND STRENGTHS
TISSEEL Kit (Freeze-Dried) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with and without the DUPLOJECT System.
TISSEEL Pre-Filled Syringe (Frozen) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with the DUO Set.

4 CONTRAINDICATIONS
4.1 Intravascular Application
Do not inject TISSEEL directly into the circulatory system or into highly vascularized tissue. Intravascular application of TISSEEL can lead to intravascular coagulation, can result in life-threatening thromboembolic events, and can increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients *(*see *Warnings and Precautions (5.3)* and *Adverse Reactions (6.2)).*

4.2 Aprotinin Hypersensitivity
Do not use TISSEEL in individuals with a known hypersensitivity to aprotinin *(see Warnings and Precautions (5.1) and Adverse Reactions (6)).*

4.3 Severe or Brisk Bleeding
Do not use TISSEEL for treatment of severe or brisk arterial or venous bleeding. In these situations, TISSEEL will be washed away in the flow of blood before hemostasis can be attained.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity/Allergic/Anaphylactic Reactions
Hypersensitivity or allergic/anaphylactoid reactions can occur with the use of TISSEEL. Cases (<1/10,000) have been reported in post marketing experience with Baxter's fibrin sealant *(see Adverse Reactions (6.2)).* In specific cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if TISSEEL is applied repeatedly over time or in the same setting, or if systemic aprotinin has been administered previously. Even if the first treatment was well tolerated, this may not exclude the occurrence of an allergic reaction after a subsequent administration of TISSEEL or systemic aprotinin. Observed symptoms of allergic anaphylactic reactions to TISSEEL have included: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnea, nausea, urticaria, angioedema, pruritus, erythema and paresthesia. Such reactions can also occur in patients receiving TISSEEL for the first time.

Aprotinin is included in TISSEEL for its antifibrinolytic properties. Aprotinin, a protein, is known to be associated with anaphylactic reactions. Even in the case of strict local application of aprotinin, there is a risk of anaphylactic reactions to aprotinin, particularly in the case of previous exposure *(see Contraindications (4.2)).* TISSEEL does not contain any substances of bovine origin.

Discontinue administration of TISSEEL in the event of hypersensitivity reactions. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy. Remove remaining product from the application site.

5.2 Application Precautions
Air or gas embolism has occurred when fibrin sealant was administered using pressurized gas. This can occur if a spray device is used at higher than recommended pressures and in close proximity to the tissue surface.

When applying TISSEEL using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 20-25 psi. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism. When using the EASYSPRAY device, or an equivalent spray device for open surgical procedures cleared by FDA, TISSEEL must not be sprayed in enclosed body areas and must be sprayed onto only visible application sites.

The sealer protein and thrombin solutions are denatured by alcohol, iodine or heavy metal ions. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before the application of TISSEEL.

Apply TISSEEL as a thin layer as excess clot thickness can negatively interfere with wound healing.

5.3 Use in Surgery

To minimize the risk of intravascular application, exercise caution when using TISSEEL in surgery (*see Contraindications (4.1) and Adverse Reactions (6.2)).*

5.4 Use in Neurosurgical Procedures
The safety and effectiveness of TISSEEL used alone or in combination with biocompatible carriers in neurosurgical procedures or other surgeries involving confined spaces have not been evaluated, and its use in this setting is not approved by FDA *(see Adverse Reactions (6.2) and Drug Interactions (7)).*

5.5 Infection Risk from Human Plasma
TISSEEL is made from human plasma. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically the Creutzfeldt-Jakob disease (CJD) agent.
All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, telephone # 1-866-888-2472.

6 ADVERSE REACTIONS
Hypersensitivity or allergic/anaphylactoid reactions have occurred. In isolated cases, these reactions have progressed to severe anaphylaxis (*see Warnings and Precautions (5.1)*). No adverse events of this type were reported during clinical trials.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Increased D-Dimer levels have been observed during a clinical study in cardiovascular surgery *(see Clinical Studies (14)),* but did not exceed values reported in the literature occurring after this type of surgery. Postoperatively increased D-Dimers can result at least partly from the degradation of Fibrin Sealant.

There were no reports of serious, associated adverse reactions reported above 1% in clinical studies.

6.2 Post-Marketing Experience
Because adverse reactions are reported voluntarily and the population is of uncertain size, it is not always possible to reliably estimate the frequency of these reactions.

The following adverse reactions have been reported in the post-marketing experience.

IMMUNE SYSTEM DISORDERS: Hypersensitivity, including anaphylactic reaction and anaphylactic shock. Anaphylactic reactions and anaphylactic shock have included fatal outcomes.
VASCULAR DISORDERS: hypotension, thromboembolism, including cerebral artery embolism, cerebral infarction*
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: angioedema, erythema, impaired wound healing, pruritus, urticaria
CARDIAC DISORDERS: bradycardia, tachycardia
RESPIRATORY DISORDERS: bronchospasm, dyspnea, wheezing
GASTROINTESTINAL DISORDERS: nausea
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: flushing, paresthesia
* as a result of intravascular application into the superior petrosal sinus

Class Effect: Air embolism has occurred with misapplication of fibrin sealant using the spray device. A post marketing fatality was reported in association with the use of another fibrin sealant when applied using a spray device. The case involved an attempt to stop active bleeding by applying the fibrin sealant using a spray device attached to a wall unit at a higher than recommended pressure for the spray device. In addition, the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant. The patient suffered a fatal air embolism.

Manifestations of hypersensitivity or allergic reactions associated with the class of fibrin sealant/hemostatic products include: application site irritation, chest discomfort, chills, headache, lethargy, restlessness and vomiting. There have been no reports of these reactions related to the specific use of TISSEEL

There have been reports of serious adverse events such as paralysis and other compressive complications possibly related to the use of fibrin sealants in combination with resorbable hemostatic agents. There have also been reports of fatalities following the misadministration of topical thrombin *(see Warnings and Precautions (5.4)).*

7 DRUG INTERACTIONS
Oxidized cellulose-containing preparations can reduce the efficacy of TISSEEL and should not be used as carrier materials.
No interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Animal reproduction studies have not been conducted with TISSEEL. It is also not known whether TISSEEL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection). TISSEEL should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TISSEEL is administered to nursing mothers.

8.4 Pediatric Use

Limited clinical study data are available with regard to the use of TISSEEL in children. Of 365 patients undergoing repeated cardiac surgery or emergency resternotomy in a clinical trial of TISSEEL, 27 pediatric patients aged 16 years or younger were treated with TISSEEL. Of these, 2 patients were less than 6 months, 2 patients were between the ages of 6 months and 2 years, 15 patients were between 3-11 years of age, and 8 patients were between 12-16 years of age. There were no differences in safety observed between these subjects and the overall population. (see *Clinical Studies (14)).*

8.5 Geriatric Use

Clinical studies included 218 patients aged 65 years of age or older treated with TISSEEL (159 undergoing cardiac surgery and 59 undergoing vascular surgery) *(see Clinical Studies (14)).* No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

TISSEEL [Fibrin Sealant] is a two-component fibrin sealant made from pooled human plasma. When combined, the two components, Sealer Protein and Thrombin mimic the final stage of the blood coagulation cascade.

Sealer Protein (Human)

Sealer Protein (Human) is a sterile, non-pyrogenic, vapor heated and solvent/detergent treated preparation made from pooled human plasma. Sealer Protein (Human) is provided either as a freeze-dried powder for reconstitution with Fibrinolysis Inhibitor Solution or as a finished frozen solution pre-filled into one side of a dual-chambered syringe. The active ingredient in Sealer Protein (Human) is fibrinogen. Sealer Protein (Human) solution contains fibrinolysis inhibitor, synthetic Aprotonin, that delays fibrinolysis. Aprotinin (Synthetic) is manufactured by solid phase synthesis from materials completely of non-human/non-animal origin.

Thrombin (Human)

Thrombin (Human) is a sterile, non-pyrogenic, vapor heated and solvent/detergent treated preparation made from pooled human plasma. Thrombin (Human) is also provided either as a freeze-dried powder for reconstitution with Calcium Chloride Solution or as a finished frozen solution pre-filled into one side of a dual-chambered syringe.

The reconstituted solution or pre-filled syringe contains:

Sealer Protein Solution

Total protein: 96 – 125 mg/mL
Fibrinogen: 67 – 106 mg/mL
Aprotinin (Synthetic): 2250 – 3750 KIU/mL
Other ingredients include: human albumin, tri-sodium citrate, histidine, niacinamide, polysorbate 80 and water for injection.

Thrombin Solution

Thrombin (Human): 400 – 625 units/mL*
Calcium Chloride: 36 – 44 µmol/mL
Other ingredients include: human albumin, sodium chloride and water for injection.

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

11.1 Viral Clearance

TISSEEL is made from pooled human plasma collected at US licensed collection centers. The vapor heat and solvent/detergent treatment steps used in the manufacturing process have been shown to be capable of significant viral reduction. No procedure, however, has been shown to be completely effective in removing viral infectivity from derivatives of human plasma (*see Warnings and Precautions (5.5)).* Validation studies were conducted using samples drawn from manufacturing intermediates for each of the two human plasma derived components. These samples were spiked with stock virus suspensions of known titers followed by further processing under conditions representative of respective manufacturing steps.

The virus reduction factors (expressed as $\log_{10}$) of manufacturing steps for each of the viruses tested are shown in Table 5.

Table 5: Reduction Factors for Virus Removal and/or Inactivation

Sealer Protein Component					
Manufacturing Step	Mean Reduction Factors [$\log_{10}$] of Virus Tested				
	HIV-1	HAV	BVDV	PRV	MMV
Early Manufacturing Steps	n.d.	n.d.	n.d.	n.d.	2.7
Solvent/Detergent Treatment	>5.3	n.d.	>5.7	>5.9	n.d.
Vapor Heat Treatment	>5.5	>5.6	>5.7	>6.7	1.2
Overall Reduction Factor (ORF)	>10.8	>5.6	>11.4	>12.6	3.9
Thrombin Component					
Manufacturing Step	Mean Reduction Factors [$\log_{10}$] of Virus Tested				
	HIV-1	HAV	BVDV	PRV	MMV
Thrombin Precursor Mass Capture	3.2	1.5	1.8	2.5	1.2
Vapor Heat Treatment	>5.5	>4.9	>5.3	>6.7	1.0
Solvent/Detergent Treatment	>5.3	n.d.	>5.5	>6.4	n.d.
Ion Exchange Chromatography	n.d.	n.d.	n.d.	n.d.	3.6
Overall Reduction Factor (ORF)	>14.0	>6.4	>12.6	>15.6	5.8

n.d. = not determined

HIV-1: Human Immunodeficiency Virus 1; **HAV**: Hepatitis A Virus; **BVDV**: Bovine Viral Diarrhea Virus, a model for Hepatitis C Virus; **PRV**: Pseudorabies Virus, a model for lipid enveloped DNA viruses, among those is Hepatitis B Virus; **MMV**: Mouse Minute Virus, a model for B19V.

In addition, Human Parvovirus B19 (B19V) was used to investigate the upstream Thrombin precursor mass capture step, the Sealer Protein early manufacturing steps and the Thrombin and Sealer Protein vapor heating steps. Using quantitative PCR assays, the estimated B19V log reduction factors were: (a) 1.7 for the Thrombin precursor mass capture step, (b) 3.4 for Sealer Protein early manufacturing steps, (c) >4 for Thrombin vapor heat treatment and (d) 1.0 for Sealer Protein vapor heat treatment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Upon mixing Sealer Protein (Human) and Thrombin (Human), soluble fibrinogen is transformed into fibrin, forming a rubber-like mass that adheres to the wound surface and achieves hemostasis and sealing or gluing of tissues. TISSEEL mimics the final coagulation cascade step as it has all relevant components to form a clot. TISSEEL is effective in heparinized patients and in patients medicated with anti-platelet drugs.

12.2 Pharmacodynamics

Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin. Fibrinolysis inhibitor, Aprotinin (Synthetic), is a polyvalent protease inhibitor that prevents premature degradation of fibrin. Preclinical studies with different fibrin sealant preparations simulating the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of aprotinin in the product formulation increases resistance of the fibrin sealant clot to degradation in a fibrinolytic environment.

12.3 Pharmacokinetics

Unincorporated Aprotinin and its metabolites have a half-life of 30 to 60 minutes and are eliminated by the kidney. Pharmacokinetic studies were not conducted. TISSEEL is expected to be completely resorbed in 10 to14 days

Because TISSEEL is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Vascular Surgery

TISSEEL was evaluated in a prospective, controlled, randomized, single-blind, multicenter clinical study against manual compression with gauze pads in 140 subjects undergoing vascular surgery with expanded polytetrafluoroethylene (ePFTE) graft placement (arterio-arterial bypasses and AV shunts for dialysis access in the upper and lower extremity). Subjects received standardized dosages of heparin. Protamine was administered after the primary endpoint had been assessed. Long-term antiplatelet treatments were continued perioperatively at the surgeon's discretion.

Subjects were randomly assigned to TISSEEL or control when persistent bleeding at the study suture line was present after surgical hemostasis, i.e., sutures. Eligible bleedings before clamping and treatment application were defined as a minimum of 25% of the suture line bleeds or at least 5 suture line bleedings or any pulsatile or spurting needle hole bleeding. For the primary endpoint, hemostasis achieved at the study suture line at 4 minutes and maintained until surgical closure, a single application of TISSEEL was statistically significantly superior to control (p<0.0001; likelihood ratio chi-square test; 2.5% one sided) [ITT].

Table 6: Vascular Surgery

Hemostasis at the study suture line within 4 minutes and maintained until surgical closure		
	TISSEEL	Manual Compression
Intent to Treat Analysis	44/70 (62.9%)	22/70 (31.4%)

14.2 Cardiac Surgery

TISSEEL was evaluated in a prospective, parallel design, randomized (1:1), double-blind, multicenter clinical study against an earlier formulation of the product, TISSEEL VH, in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) and median sternotomy. Patients were treated with TISSEEL or the control product only when hemostasis was not achieved by conventional surgical methods. For the endpoint, hemostasis achieved at the primary treatment site within 5 minutes of treatment and maintained until closure of the surgical wound, TISSEEL was non-inferior to the earlier formulation of the product using a one-sided 97.5% confidence interval on the difference in the proportion of subjects successfully treated.

Table 7: Cardiac Surgery

Hemostasis within 5 minutes and maintained until surgical closure		
	TISSEEL	TISSEEL VH
Intent to Treat Analysis	127/144 (88.2%)	129/144 (89.6%)

14.3 Cardiac Reoperations

An earlier formulation of TISSEEL was evaluated in an open-label crossover study against control topical hemostatic agents in 489 patients undergoing cardiovascular reoperation or resternotomy at 11 institutions. Patients were randomized to TISSEEL or control hemostatic agents when a topical hemostatic was needed at the conclusion of surgery and after all attempts at surgical hemostasis. Patients were crossed to the alternative therapy if bleeding continued after the 5 minute endpoint. At 10 centers, TISSEEL was used after administration of protamine sulfate. At one site, TISSEEL could be used before administration of protamine sulfate. 365 of the 489 patients developed bleeding episodes requiring treatment. For the endpoint (successful hemostasis at 5 minutes), TISSEEL was statistically significantly superior to control topical hemostatic agents in these patients. Similarly, absolute time to cessation of bleeding was statistically significantly shorter for TISSEEL than for control topical hemostatic agents (p<0.0001, Gehan-Wilcoxon test, two sided).

Table 8: Cardiac Reoperations

Hemostasis within 5 minutes	
TISSEEL	Control Topical Hemostatic Agent
82.4% (159/193)	44.5% (76/172)
Pearson χ^2 two sided; p <0.0001; intent-to-treat analysis	

14.4 Splenectomy

In a single center, open label trial, an earlier formulation of TISSEEL was compared to historical controls in patients undergoing laparotomy for blunt or penetrating traumatic injury to the spleen and/or liver. Use of TISSEEL resulted in the need for statistically significantly fewer splenectomies than control hemostatic maneuvers (Refer to Table 9). TISSEEL did not result in significantly reduced mortality in patients with blunt or penetrating trauma to the liver alone or to the liver and spleen (p=0.067, χ^2, one sided).

Table 9: Splenectomy

Splenectomy Rate			
Injury to:	TISSEEL	Historic Controls	
Spleen	0/19	14/22	p <0.001
Spleen and liver	1/26	19/34	p <0.001

14.5 Colostomy Closure

In a single center, prospective open label study of 118 patients randomized to standard of care (58 patients) or standard of care plus fibrin sealant (60 patients) for elective colostomy closure after temporary colostomy placement for treatment of traumatic injury to the colon, the earlier version of TISSEEL plus standard of care was also shown to be significantly superior to standard of care alone (p=0.0406, Jonckheere-Terpstra test for ordinal data, two sided) with regard to anastomotic complications (leakage, intra-abdominal abscess formation, re-operation, septic shock, and death).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TISSEEL is supplied in the following pack sizes and presentations:

Table 10: NDC Numbers

Pack Size	TISSEEL Kit (Freeze-Dried)	TISSEEL Kit (Freeze-Dried) with DUPLOJECT System	TISSEEL Pre-Filled Syringe (Frozen) with DUO Set
2 mL	0944-4210-02	0944-4301-02	0944-8402-02
4 mL	0944-4211-04	0944-4302-04	0944-8402-04
10 mL	0944-4212-10	0944-4303-10	0944-8402-10

TISSEEL Kit contains one vial each of:
1. Sealer Protein Concentrate (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile
2. Fibrinolysis Inhibitor Solution, (Synthetic) Liquid, Sterile
3. Thrombin (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile
4. Calcium Chloride Solution, Liquid, Sterile

TISSEEL Pre-Filled Dual-Chambered Syringe contains:
1. Sealer Protein Solution, Vapor Heated, Solvent/Detergent Treated, Frozen Solution, Sterile
2. Thrombin Solution, Vapor Heated, Solvent/Detergent Treated, Frozen Solution, Sterile
3. Sterile accessory devices (DUO Set: 1 plunger, 2 joining pieces and 4 application cannulas)

Storage

TISSEEL Kit (Freeze-Dried)

Store at 2-25°C. Avoid freezing. Do not freeze or refrigerate reconstituted solutions.

TISSEEL Pre-filled Syringe (Frozen)

Store at ≤ -20°C. Do not refrigerate or re-freeze after thawing.

Do not use after the expiration date. Discard if packaging of any components is damaged.

17 PATIENT COUNSELING INFORMATION

Discuss the risks and benefits of this product with the patient since it is made from human plasma.

Instruct patients to consult their physician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose) followed about two weeks later by a rash and joint pain (s*ee Use in Specific Populations (8.1)).*

Baxter Healthcare Corporation
Westlake Village, CA 91362 USA
US License No. 140

This product is covered by US Patent No. 5,962,405.
Baxter, Duo, Duploject, Easyspray, Fibrinotherm and Tisseel are trademarks of Baxter International Inc.

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-244.10.08

Product Service

EC Certificate

Full Quality Assurance System
Directive 93/42/EEC on Medical Devices (MDD), Annex II excluding (4)
(Devices in Class IIa, IIb or III)

No. G1 062680 0155 Rev. 00

Manufacturer: **Baxter Healthcare SA**
8010 Zürich
SWITZERLAND

Facility(ies): **Baxter Healthcare S.A.**
Thurgauerstrasse 130, 8152 Glattpark (Opfikon),
SWITZERLAND

Product Category(ies): **Single use devices and pressure regulator including accessory for the application of surgical sealants**

The Certification Body of TÜV SÜD Product Service GmbH declares that the aforementioned manufacturer has implemented a quality assurance system for design, manufacture and final inspection of the respective devices / device categories in accordance with MDD Annex II. This quality assurance system conforms to the requirements of this Directive and is subject to periodical surveillance. For marketing of class III devices an additional Annex II (4) certificate is mandatory. See also notes overleaf.

Report No.: **713163333**

Valid from: 2020-02-21
Valid until: 2024-05-26

Date, 2020-02-21

Head of Certification/Notified Body

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT
TÜV SÜD
A4 / 07.17

Declaration of Conformity

According to:	**Council Directive 93/42/EEC (MDD)**
Annexes: II, excluding 4	
Notified Body Certificate(s): G1 062680 0155 Rev.00	
Notified Body's name and address: Notified Body's identification number:	TÜV SÜD Product Service GmbH Ridlerstraße 65 80339 Munich Germany 0123
Manufacturer's name:	Baxter Healthcare SA
Manufacturer's address:	8010 Zürich Switzerland
EC Representative's address: not applicable	
+++We declare under our sole responsibility that the following product(s) conform to the applicable provisions of the above-mentioned Directive:+++	
Product Family/Category:	Single use devices and pressure regulator including accessory for the application of surgical sealants
Code Numbers:	See "CE Marked Product Code List"

+++This declaration is made on the following basis:

- The validity of this document shall not start earlier than the validity date of the corresponding EC Certificate.
- The DOC declares conformity to all product lots released within the above validity period.
- For Class I non-sterile / non-measuring: self-declaration of conformity.
- Compliance to standards and regulations as defined in the Technical Documentation and Essential Requirements Checklist.+++

Signature

CE-marked Product Code List
to the Declaration of Conformity

Business: Advanced Surgery

Certificate Number:	G1 062680 0155
Conformity Assessment Procedure:	Annex II, excluding (4)
Classification:	IIa
Sterilisation Method:	Gamma, ETO, n.a.
Facility:	Lessines (Belgium)
Product Category:	Single use devices and pressure regulator including accessory for the application of surgical sealants

Code	Description	Date of CE marking
1502323	DUPLOCATH 25	see BaxTRACs
1502324	DUPLOCATH 35 MIS	see BaxTRACs
1502325	DUPLOCATH 180	see BaxTRACs
3400662	DUPLOJECT System 2ml/4ml	see BaxTRACs
3400663	DUPLOJECT System 10ml	see BaxTRACs
3400666	DUPLOJECT Combi	see BaxTRACs
3400667	DUPLOJECT Combi P	see BaxTRACs
3400658	DUO Set A 2ml/4ml	see BaxTRACs
3400659	DUO Set A 10ml	see BaxTRACs
3400654	DUO Set 2ml/4ml	see BaxTRACs
3400655	DUO Set 10ml	see BaxTRACs
1504720	EASYSPRAY 2 bar, CE	see BaxTRACs
1502696	EASYSPRAY Air 800	see BaxTRACs
1504272	TISSEEL/ARTISS Spray Set (10 pack)	see BaxTRACs
1504273	TISSEEL/ARTISS Spray Set (single pack)	see BaxTRACs
1504271	TISSEEL/TISSUCOL Spray Set	see BaxTRACs
0600021	COSEAL Spray Set	see BaxTRACs

This report has been reviewed and verified by: [redacted]

Title: Germany Adv Surg Regulatory

TÜV SÜD Product Service GmbH · Ridlerstrasse 65 · 80339 Munich · Germany

Product Service

Add value.
Inspire trust.

Baxter Healthcare SA
Thurgauerstrasse 130
8152 GLATTPARK (OPFIKON)
SWITZERLAND

Your reference/letter of	Our reference/name	Tel. extension/Email	Fax extension	Date	Page
56740	713257648	medical_devices@tuvsud.com		2024-04-02	1 of 4

TÜV SÜD Product Service GmbH
Confirmation Letter
CL 056740 0062 Rev. 00

Reference: 713257648

To whom it may concern,

Confirmation of the status of a formal application, written agreement, and appropriate surveillance in the framework of Regulation EU 2023/607 amending Regulations (EU) 2017/745 (in the following referenced as MDR) as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices.

With this letter TÜV SÜD Product Service GmbH, designated under MDR and identified by the number 0123 on NANDO, confirms that we have received a formal application in accordance with Section 4.3, first subparagraph of Annex VII of MDR and has signed a written agreement in accordance with Section 4.3, second subparagraph of Annex VII of MDR with the above stated manufacturer with the following SRN Number:

SRN Number**: CH-MF-000026124**

The devices covered by the formal application and the written agreement mentioned above are identified in the Tables below.

- Table 1 identifies the devices for which an MDR application has been received, written agreement concluded and for which TÜV SÜD Product Service GmbH is also responsible for appropriate surveillance of the corresponding devices under the applicable Directive.
- Table 2 identifies the devices for which an MDR application has been received and a written agreement concluded, but TÜV SÜD Product Service GmbH has not yet taken the responsibility for appropriate surveillance of the corresponding devices under the applicable Directive.

Product Service

If devices covered by certificates issued under Directive 90/385/EEC (AIMDD) or Directive 93/42/EEC (MDD) that expired after 26 May 2021 and before 20 March 2023, without having been withdrawn, this letter also confirms that

- the manufacturer signed the written agreement under MDR by the date of MDD/AIMDD certificate expiry; or
- provided evidence that a competent authority of a Member State had granted a derogation or exemption from the applicable conformity assessment procedure in accordance with Article 59(1) of MDR or Article 97(1) of the MDR respectively.

The transition timelines in accordance Article 120 (3) of MDR that apply to the devices covered by this letter, subject to the manufacturer's continued compliance to the other conditions specified in Article 120 (3c) of MDR, are shown below:

- 26 May 2026 for Class III custom-made implantable devices
- 31 December 2027 for Class III devices and Class IIb implantable devices (except sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors)
- 31 December 2028 for other Class IIb devices, Class IIa, Class I devices placed on the market in sterile condition, measuring function
- 31 December 2028 for devices not requiring the involvement of a notified body under MDD but requiring it under MDR (e.g., class I devices that qualify as re-usable surgical instruments)

We reserve the right to invoice any issuance, copies, amendments and / or changes of the confirmation letter according to effort.

For confirmation letter validity see www.tuvsud.com/ps-cert?q=cert: CL 056740 0062 Rev. 00

In case of inquiries please contact medical_devices@tuvsud.com.

On behalf of the Notified Body TÜV SÜD Product Service GmbH,
2024-02-02

TÜV SÜD Product Service GmbH	TÜV SÜD Product Service GmbH
Conformity Assessment Responsible (CARE)	Application Reviewer

Product Service

Table 1: Devices covered by this letter and for which TÜV SÜD Product Service GmbH is also responsible for appropriate surveillance of the corresponding devices under the applicable Directive:

Device name or Basic UDI-DI (under MDR application)	MDR Device classification (as proposed by the manufacturer and verified during application review)	If the MDR device is a substitute device, identification of the corresponding MDD/AIMDD device	MDD/AIMDD Certificate Reference(s) of the devices under MDR application, and the NB Identification
Duploject Combi **00854120000000000000037J9**	☐ Class III ☐ Class IIb implantable (non-exempted) ☐ Class IIb / Class IIb implantable (exempted) ☒ Class IIa ☐ Class I devices in sterile condition ☐ Class I devices with measuring function ☐ Class III implantable custom-made-device	☒ N/A or ☐ Identification of the corresponding device under MDD/AIMDD Individual Article number:	☒ Certification as follows: Certificate # G1 0626800155 Rev.00; NB# 0123 or ☐ Evidence that a competent authority of a Member State had granted acc. MDR, Art.59 (1) or Art.97 (1) Evidence #1; CA# Evidence #2; CA#
Duplocath Application Catheter 35 M.I.S. **Duplocath Application Catheter 25** **Duplocath Application Catheter 180** **00854120000000000000159JQ**	☐ Class III ☐ Class IIb implantable (non-exempted) ☐ Class IIb / Class IIb implantable (exempted) ☒ Class IIa ☐ Class I devices in sterile condition ☐ Class I devices with measuring function ☐ Class III implantable custom-made-device	☒ N/A or ☐ Identification of the corresponding device under MDD/AIMDD Individual Article number:	☒ Certification as follows: Certificate # G1 0626800155 Rev.00; NB# 0123 or ☐ Evidence that a competent authority of a Member State had granted acc. MDR, Art.59 (1) or Art.97 (1) Evidence #1; CA# Evidence #2; CA#
Duploject System 10 ml **Duploject System 2 ml/4 m** **00854120000000000000161JB**	☐ Class III ☐ Class IIb implantable (non-exempted) ☐ Class IIb / Class IIb implantable (exempted) ☒ Class IIa ☐ Class I devices in sterile condition ☐ Class I devices with measuring function ☐ Class III implantable custom-made-device	☒ N/A or ☐ Identification of the corresponding device under MDD/AIMDD Individual Article number:	☒ Certification as follows: Certificate # G1 0626800155 Rev.00; NB# 0123 or ☐ Evidence that a competent authority of a Member State had granted acc. MDR, Art.59 (1) or Art.97 (1) Evidence #1; CA#

Product Service

Device name or Basic UDI-DI (under MDR application)	MDR Device classification (as proposed by the manufacturer and verified during application review)	If the MDR device is a substitute device, identification of the corresponding MDD/AIMDD device	MDD/AIMDD Certificate Reference(s) of the devices under MDR application, and the NB Identification
			Evidence #2; CA#
Coseal Spray Set **Tisseel / Artiss Spray Set** **00854120000000000100013J8**	☐ Class III ☐ Class IIb implantable (non-exempted) ☐ Class IIb / Class IIb implantable (exempted) ☒ Class IIa ☐ Class I devices in sterile condition ☐ Class I devices with measuring function ☐ Class III implantable custom-made-device	☒ N/A or ☐ Identification of the corresponding device under MDD/AIMDD Individual Article number:	☒ Certification as follows: Certificate # G1 0626800155 Rev.00; NB# 0123 or ☐ Evidence that a competent authority of a Member State had granted acc. MDR, Art.59 (1) or Art.97 (1) Evidence #1; CA# Evidence #2; CA#

Table 2: Devices covered by this letter and for which TÜV SÜD Product Service GmbH is <u>NOT</u> responsible for appropriate surveillance of the corresponding devices under the applicable Directive:

Device name or Basic UDI-DI (under MDR application)	MDR Device classification (as proposed by the manufacturer and verified during application review)	If the MDR device is a substitute device, identification of the corresponding MDD/AIMDD device	MDD/AIMDD Certificate Reference(s) of the devices under MDR application, and the NB Identification

Confirmation Letter Version History

Date	TÜV SÜD Product Service GmbH internal reference traceable to each version of the letter	Action
2024/04/02	713257648	Initial issue