

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TISSEEL Lyo – Powders and solvents for sealant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1: Sealer protein solution

Sealer protein concentrate, lyophilized (Tisseel powder), reconstituted with aprotinin solution

Human fibrinogen (as clottable protein) 91 mg¹/ml
Aprotinin (synthetic) 3000 KIU²/ml

Excipient(s) with known effect:
Polysorbate 80 0.6 – 1.9 mg/ml

Component 2: Thrombin solution

Thrombin, lyophilized, reconstituted with calcium chloride solution

Human thrombin 500 IU³/ml
Calcium chloride dihydrate 40 µmol/ml

1, 2 or 5 ml sealer protein solution and 1, 2 or 5 ml thrombin solution combine to make 2, 4 or 10 ml ready-to-use solution.

After mixing	1 ml	2 ml	4 ml	10 ml
Component 1: Sealer protein solution				
Human fibrinogen (as clottable protein)	45.5 mg	91mg	182 mg	455 mg
Synthetic Aprotinin	1500 KIU	3000 KIU	6000 KIU	15000 KIU
Component 2: Thrombin solution				
Human thrombin	250 IU	500 IU	1000 IU	2500 IU
Calcium chloride dihydrate	20 µmol	40 µmol	80 µmol	200 µmol

TISSEEL Lyo contains Human Factor XIII co-purified with Human Fibrinogen in a range of 0.6 – 5 IU/ml.

For the full list of excipients, see section 6.1.

¹ Contained in a total protein concentration of 96 – 125 mg/ml

² 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)

³ Thrombin activity was determined using the current WHO Standard for thrombin.

3. PHARMACEUTICAL FORM

Powders and solvents for sealant

Freeze-dried constituents are hygroscopic, white or pale yellow powders or friable solids; liquid constituents are clear, colorless or slightly yellowish solutions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment where standard surgical techniques appear insufficient (see point 5.1)

- For improvement of hemostasis
- As a tissue glue to improve wound healing or to support sutures in vascular surgery and in gastrointestinal anastomoses.
- For tissue sealing, to improve adhesion of the separated tissue (e.g. tissue flaps, grafts, split skin grafts [mesh grafts]).

The efficacy in fully heparinized patients has been proven.

4.2 Posology and method of administration

The use of TISSEEL Lyo is restricted to experienced surgeons who have been trained in the use of TISSEEL Lyo.

Posology

The amount of TISSEEL Lyo to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including the type of surgical intervention, the size of the affected area and the mode of intended application, and the number of applications.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 4 to 20 ml. For some procedures (e.g. liver traumata, or the sealing of large burned surfaces), larger volumes may be required.

The initial amount of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary. However, avoid reapplication of TISSEEL Lyo to a pre-existing polymerized TISSEEL Lyo layer as TISSEEL Lyo will not adhere to a polymerized layer.

As a guideline for the gluing of surfaces, 1 pack of TISSEEL Lyo 2 ml (i.e. 1 ml Tisseel solution plus 1 ml thrombin solution) will be sufficient for an area of at least 10 cm².

When TISSEEL Lyo is applied by spray application the same quantity will be sufficient to coat considerably larger areas, depending on the specific indication and the individual case.

It is recommended that, to avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, as thin a layer as possible of TISSEEL Lyo should be applied.

Paediatric population

The safety and efficacy of TISSEEL Lyo in paediatric patients have not been established.

Method of administration

For epilesional use.

Prepare the solutions as described at 6.6.

In order to ensure optimal safe use of TISSEEL Lyo by spray application the following recommendations should be followed:

In open wound surgery - a pressure regulator device that delivers a maximum pressure of no more than 2.0 bar (28.5 psi) should be used.

In minimally invasive/laparoscopic procedures – a pressure regulator device that delivers a maximum pressure of no more than 1.5 bar (22 psi) and uses carbon dioxide gas only should be used.

Prior to applying TISSEEL Lyo the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

TISSEEL Lyo must be sprayed only onto application sites that are visible.

TISSEEL Lyo should only be reconstituted and administered according to the instructions and with the devices recommended for this product (see section 6.6).

For spray application, see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure and length of applicator tips.

In surgical procedures that require the use of minimal volumes of fibrin sealant, it is recommended to expel and discard the first few drops of product.

4.3 Contraindications

TISSEEL Lyo alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.

TISSEEL Lyo is not indicated to replace skin sutures intended to close surgical wound.

TISSEEL Lyo must never be applied intravascularly. Intravascular application may result in life-threatening thromboembolic events.

TISSEEL Lyo must not be applied in case of hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly.

Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

Caution must be used when applying fibrin sealant using pressurized gas.

Any application of pressurized gas is associated with a potential risk of air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening.

Apply TISSEEL Lyo as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO₂ and therefore cannot be excluded with TISSEEL Lyo when sprayed in open wound surgery.

When applying TISSEEL Lyo using a spray device, be sure to use a pressure within the pressure range recommended by the spray device manufacturer (see table in section 6.6 for pressures and distances).

TISSEEL Lyo spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer. Do not spray closer than the recommended distances.

When spraying TISSEEL Lyo, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism (also see section 4.2).

TISSEEL Lyo must not be used with the Easy Spray / Spray Set system in enclosed body areas.

Before the administration of TISSEEL Lyo, care is to be taken that parts of the body outside the designated application area are sufficiently protected/covered to prevent tissue adhesion at undesired sites.

If fibrin sealants are applied in confined spaces, e.g. the brain or the spinal cord, the risk of compressive complications should be taken into account.

To ensure adequate mixing of the sealer protein component and the thrombin component, the first few drops of the product from the application cannula should be expelled and discarded immediately before use.

As with any protein-containing product, allergic type hypersensitivity reactions are possible.

Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

Hypersensitivity and anaphylactic reactions (also fatal, including anaphylactic shock) have been reported with TISSEEL Lyo. Signs of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension. If these symptoms occur, the administration must be discontinued immediately and the currently valid standard measures for the treatment of shock are to be taken. Remaining product must be removed from the site of application.

TISSEEL Lyo contains a synthetic protein (aprotinin). Even in case of strict local application, there is a risk of anaphylactic reaction linked to the presence of aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records.

As synthetic aprotinin is structurally identical to bovine aprotinin the use of TISSEEL Lyo in patients with allergies to bovine proteins should be carefully evaluated.

In two retrospective, non-randomized studies in coronary bypass surgery, patients who received fibrin sealant showed a statistically significant increased risk of mortality. While these studies could not provide a causal relationship, the increased risk associated with the use of TISSEEL in these patients cannot be excluded. Therefore, additional care should be taken to avoid inadvertent intravascular administration of this product.

Injection into the nasal mucosa must be avoided, as thromboembolic complications may occur in the area of the *arteria ophthalmica*.

Injecting TISSEEL Lyo into tissue carries the risk of local tissue damage.

TISSEEL Lyo should only be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Polysorbate 80 may cause locally limited skin irritations such as contact dermatitis.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

These measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus HAV.

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemolytic anemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived fibrin sealant.

It is strongly recommended that every time that TISSEEL Lyo is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Oxidized cellulose-containing preparations should not be used with TISSEEL Lyo (See section 6.2 Incompatibilities).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol,

iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.
See also section 6.2

4.6 Fertility, pregnancy and lactation

The safety of fibrin sealants/hemostatics for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and peri-and postnatal development.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

See section 4.4 for information on Parvovirus B19 infection.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include but are not limited to angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, breathing difficulties, transient erythema ("flushing"), generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, paresthesia, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants / hemostatics, anaphylactic reactions and anaphylactic shock have included fatal outcomes.

In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin (see section 4.4) or any other constituents of the product.

Even if repeated treatment with TISSEEL Lyo was well tolerated, a subsequent administration of TISSEEL Lyo or systemic administration of aprotinin may result in severe anaphylactic reactions.

Antibodies against components of the fibrin sealant / hemostatic may occur in rare cases.

Inadvertent intravascular injection may result in thromboembolic events and DIC.
Furthermore there is the risk of an anaphylactic reaction (see section 4.4).

For safety with respect to transmissible agents (see section 4.4).

The adverse reactions presented in this section were reported from clinical trials investigating the safety and efficacy of TISSEEL and from post-marketing experience (marked with a ^p in the adverse event table below) with Baxter Fibrin Sealants. In the clinical trials, TISSEEL was administered for adjunct hemostasis in cardiac, vascular, and total hip replacement surgeries and in liver and spleen surgeries. Other clinical trials included the sealing of lymphatic vessels in patients undergoing axillary lymph node dissection, sealing of colonic anastomosis and in dural sealing in the posterior fossa. As the frequencies of adverse events observed in post marketing experience cannot be calculated, whenever possible, the upper limit of the 95% confidence interval was calculated using the "rule of three" in the following manner: $3/1146 = 0.0026$ or 0.26% which is "Uncommon" (where "1146" is the total number

of subjects to have received TISSEEL in the clinical trials from which data were included in the SmPC).

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $<1/10$)

Uncommon ($\geq 1/1,000$ to $<1/100$)

Rare ($\geq 1/10,000$ to $<1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

System organ class (SOC)	Preferred MedDRA Term	Frequency
Infections and infestations	Postoperative wound infection	Common
Blood and lymphatic system disorders	Fibrin degradation products increased	Uncommon
Immune system disorders	Hypersensitivity reactions* ^p	Uncommon
	Anaphylactic reactions* ^p	Uncommon
	Anaphylactic shock* ^p	Uncommon
	Paresthesia ^p	Uncommon
	Bronchospasm ^p	Uncommon
	Wheezing ^p	Uncommon
	Pruritus ^p	Uncommon
	Erythema ^p	Uncommon
Nervous system disorders	Sensory disturbance	Common
Cardiac disorders	Bradycardia ^p	Uncommon
	Tachycardia ^p	Uncommon
Vascular disorders	Axillary vein thrombosis **	Common
	Hypotension	Rare
	Haematoma (NOS) ^p	Uncommon
	Embolism arterial ^p	Uncommon
	Air embolism*** ^p	Not known
	Cerebral artery embolism ^p	Uncommon
	Cerebral infarction** ^p	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea ^p	Uncommon
Gastrointestinal disorders	Nausea	Uncommon
	Intestinal obstruction ^p	Uncommon
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria ^p	Uncommon
	Impaired healing ^p	Uncommon
Musculoskeletal and connective tissue disorders	Pain in an extremity	Common
General disorders and administration site conditions	Pain	Common
	Increased body temperature	Common
	Flushing ^p	Uncommon
	Oedema ^p	Uncommon
Injury, poisoning and procedural	Procedural pain	Uncommon
	Seroma	Very common

complications	Angioedema ^P	Uncommon
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* anaphylactic reactions and anaphylactic shock have included fatal outcomes.

** as a result of intravascular application into the superior petrosal sinus.

*** as with other fibrin sealants life-threatening/fatal air or gas embolism when using devices with pressurized air or gas occurred; this event appears to be related to an inappropriate use of the spray device (e.g. at higher than recommended pressure and in close proximity to the tissue surface.)

^P Adverse events observed in post-marketing experience.

Class Reactions

Other adverse reactions associated with the fibrin sealant/hemostatic class include: manifestations of hypersensitivity include application site irritation, chest discomfort, chills, headache, lethargy, restlessness, and vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via <the national reporting system listed in Appendix V*.>

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics combinations, ATC code: B02BC30; tissue adhesives, ATC code: V03AK

The fibrin adhesion system imitates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is generated from Factor XIII by the concerted action of thrombin and calcium ions, stabilizes the clot by the cross-linking of fibrin fibres.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by anti-fibrinolytics. Aprotinin is present in TISSEEL Lyo as an antifibrinolytic to prevent premature degradation of the clot.

To prove the efficacy, *in vivo* studies with four animal models which imitated the patient situation as closely as possible, were carried out. TISSEEL was effective with regard to primary and secondary hemostasis as well as wound healing.

Clinical studies demonstrating hemostasis and suture support were conducted in a total of 213 patients (120 with TISSEEL, 93 with control) undergoing vascular surgery with ePTFE conduits, in a total of 70 patients (35 with TISSEEL, 35 with control) undergoing partial hepatic resection and in a total of 317 patients (157 with TISSEEL, 160 with a predecessor single virus inactivated form of the product as control) undergoing cardiac surgery with a cardiopulmonary bypass and median sternotomy.

Efficacy of TISSEEL as an adjunct to conventional surgical methods in sealing colonic anastomoses in trauma patients undergoing closure of temporary colostomies has been demonstrated in a randomized, controlled, prospective, single-center study conducted in 1986 in a total of 120 patients (61 with TISSEEL, 59 with control).

5.2 Pharmacokinetic properties

TISSEEL Lyo is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Pharmacokinetic studies in different species of laboratory animals were not conducted.

Fibrin sealants/hemostatics are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

Due to its nature as well as its special method of application (usually single, only in exceptional cases repeated application of a few ml) and mechanism of action (local efficacy without systemic effect or distribution to other organs and tissues), no preclinical safety data are available for TISSEEL Lyo on chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation.

Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of TISSEEL. Furthermore, no evidence for mutagenicity could be seen in appropriate *in vitro* tests. The sealer protein solution was also well tolerated *in vitro*, in human fibroblast cultures, demonstrating excellent cellular compatibility and non-cytotoxicity. Based on a detailed literature review, any negative influence or toxicity due to residual S/D reagents on TISSEEL Lyo can be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component 1: Sealer protein solution:

- Human albumin
- L-histidine
- Niacinamide
- Sodium citrate dihydrate
- Polysorbate 80 (Tween 80)
- Water for Injections

Component 2: Thrombin solution: Human albumin
Sodium chloride
Water for Injections

6.2 Incompatibilities

Oxidized cellulose-containing preparations should not be used with TISSEEL Lyo because the low pH interferes with the activity of the thrombin.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

Keep the vials in the outer carton in order to protect from light.

Use the reconstituted sterile solutions within 4 hours. Keep the reconstituted sterile solutions at 37°C or at room temperature without stirring if not used immediately. Reconstituted solutions must not be refrigerated or frozen.

6.5 Nature and contents of container

All components of TISSEEL Lyo are filled into glass containers (Tisseel powder, filling size 5 ml, in type II glass vials, all other filling sizes in type I glass vials, in accordance with Ph. Eur.). The vial containing the Tisseel powder is equipped with a magnetic stirrer.

The rubber stoppers of the Tisseel powder and the Thrombin powder are made of butyl rubber. The rubber stoppers of the Aprotinin solution and the Calcium Chloride Solution are made of halogenobutyl rubber stoppers.

Contents of package:

- 1 vial containing Tisseel powder (component 1, lyophilized, with 91 mg/ml human fibrinogen)
- 1 vial containing thrombin powder (component 2, lyophilized, with 500 IU/ml human thrombin)
- 1 vial containing aprotinin solution (solvent for component 1 with 3000 KIU/ml synthetic aprotinin)
- 1 vial containing calcium chloride solution (solvent for component 2 with 40 µmol/ml calcium chloride dihydrate)
- 1 Duploject system device set for reconstitution and application consisting of:
 - 1 Duploject two-syringe clip
 - 2 joining pieces
 - 2 disposable blue-scaled syringes for Tisseel
 - 2 disposable black-scaled syringes for thrombin
 - 4 disposable needles
 - 4 application cannulas (blunt)

Pack sizes:

TISSEEL Lyo is available in the following pack sizes: 1 x 2 ml (1 ml + 1 ml), 1 x 4 ml (2 ml + 2 ml) and 1 x 10 ml (5 ml + 5 ml).

1 ml, 2 ml or 5 ml sealer protein solution together with 1 ml, 2 ml or 5 ml thrombin solution combine to make 2 ml, 4 ml or 10 ml ready-to-use final product.

Not all pack sizes may be marketed.

The set for reconstitution and application (DUPLOJECT system) is intended for single use only. Do not re-process and/or re-sterilize!

Other accessories for application of the product can be obtained from BAXTER.

6.6 Special precautions for disposal and other handling

General

Before the administration of TISSEEL Lyo, cover all parts of the body outside the area to be treated, in order to prevent tissue adhesion at undesired sites.

To prevent TISSEEL Lyo from adhering to gloves and instruments, wet these with sodium chloride solution before contact.

The guideline for sealing surfaces is: One package of Tisseel Lyo 2 ml (i.e. 1 ml sealer protein solution plus 1 ml thrombin solution) is sufficient for a surface of at least 10 cm².

The dose required depends on the size of the surface to be sealed.

Do NOT apply the two components of TISSEEL Lyo separately. Both components must be applied together.

Preparation and reconstitution

Prior to reconstitution of the fibrin sealant components, clean the rubber stoppers of all vials.

Direct contact between disinfectant and product must be avoided (see section 4.5).

I. Preparation of the sealer protein solution (component 1)

The Tisseel powder is dissolved with the aprotinin solution to form the sealer protein solution.

Reconstitute the Tisseel powder using the FIBRINOTHERM warming and stirring device (recommended method). Alternatively, use a sterile water bath at a temperature of 33 - 37°C.

Reconstitution using the FIBRINOTHERM device:

The FIBRINOTHERM device maintains a constant temperature of 37°C. It also shortens the dissolution time of the Tisseel powder by rotating the magnetic stirrer contained in each vial with Tisseel powder.

- Place the vials containing Tisseel powder and aprotinin solution into the appropriate openings of the FIBRINOTHERM device and preheat the vials for approximately 3 minutes.
- Transfer the aprotinin solution into the vial containing the Tisseel powder using one cannula and the blue-scaled syringe provided in the sterile kit for reconstitution. Place the vial containing the Tisseel powder in the stirring well of the FIBRINOTHERM device (use an appropriate adaptor, if necessary) and stir until the powder is dissolved completely. Reconstitution is complete as soon as no particles are visible when holding the vial against the light. If particles are present, keep on stirring the solution at 37°C for a few more minutes until the powder is dissolved completely. Turn off the magnetic stirrer when dissolution is complete.

Note: Do not over-stir - excessive stirring may compromise product quality!

- Keep the sealer protein solution at 37°C without stirring if it is not used immediately. To ensure homogeneity, briefly stir or swirl the sealer protein solution before drawing it up into the blue-scaled syringe provided in the double-sterile kit for application.
- Withdraw the reconstituted sealer protein solution from the vial under sterile conditions.

For further instructions please refer to the instructions for use of the FIBRINOTHERM device.

Reconstitution using a water bath:

- Preheat the vials containing the Tisseel powder and the aprotinin solution for approximately 3 minutes in a water bath at a temperature of 33 - 37°C. (Never heat beyond 37°C !)
- Transfer the aprotinin solution into the vial containing the Tisseel powder using one cannula and the blue-scaled syringe provided in the sterile kit for reconstitution.
- Return the vial containing the Tisseel powder to the water bath at 33 - 37°C for one minute.
- Swirl briefly but avoid frothing as far as possible. Then return the vial to the water bath and check periodically for complete dissolution. Reconstitution is complete as soon as no particles are visible when holding the vial against the light. If particles are present, keep the vial at a temperature of 33 - 37°C for a few more minutes and agitate until completely dissolved.
- After complete dissolution, keep the sealer protein solution at a temperature of 33 - 37°C if not used immediately. To ensure homogeneity, briefly swirl the sealer protein solution before drawing it up into the blue-scaled syringe provided in the double-sterile kit for application.
- Withdraw the reconstituted sealer protein solution from the vial under sterile conditions.

Note: When using a water bath for reconstitution instead of the FIBRINOTHERM device, always take special care not to submerge the vial, particularly the septum, to avoid contamination.

II. Preparation of the thrombin solution – (component 2)

Dissolve the thrombin powder in the calcium chloride solution to form the thrombin solution. Transfer the contents of the vial containing the calcium chloride solution into the thrombin vial. Use the second cannula and the black-scaled syringe provided in the sterile kit for reconstitution.

Swirl briefly to dissolve the lyophilized substance. To warm the thrombin solution, use either the FIBRINOTHERM device or a water bath. Keep the thrombin solution at a temperature of 33 - 37°C until use. Prior to use, draw up the thrombin solution using the second cannula and the black-scaled syringe provided in the double-sterile kit for application.

Note: Never re-use syringes and cannulas used for the reconstitution of one component for reconstitution of the other component, as this would lead to premature solidification of that component in the vial or syringe.

III. Use of reconstituted fibrin sealant components

Both fibrin sealant components must be used within 4 hours of reconstitution. Do not cool or freeze the solutions after reconstitution.

The sealer protein and thrombin solutions should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits. Before use, check the reconstituted solutions visually for particles, discoloration or other changes in its appearance. If one of the above occurs, dispose of the solutions.

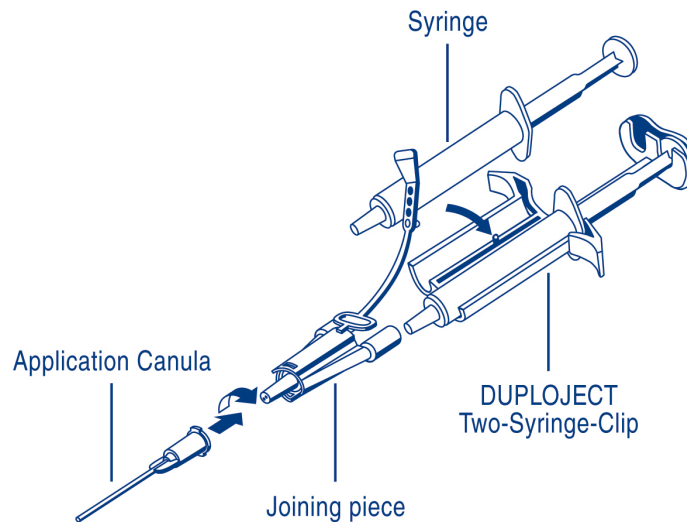
Warm TISSEEL Lyo to 33 - 37°C before application.

Do NOT expose TISSEEL Lyo to temperatures above 37°C. Do NOT microwave.

For application, place the two single-use syringes with the reconstituted sealer protein solution and thrombin solution in the DUPLOJECT Two-Syringe Clip and connect this assembly to a joining piece and an application cannula. All necessary devices are provided in the double-sterile kit for application.

The common plunger of the DUPLOJECT Two-Syringe Clip ensures that equal volumes of the two sealant components are fed through the joining piece into the application cannula where they are blended and then applied.

Operating instructions



- Place the two syringes with the sealer protein solution and with the thrombin solution into the clip. Both syringes must be filled with equal volumes.
- Expel all air from the syringe prior to attaching any application device.
- Align the joining piece and tether to the side of the syringe with the tether strap attachment point
- Connect the nozzles of both syringes to the joining piece ensuring that they are firmly attached.
 - Secure the joining piece by fastening the tether strap to the DUPLOJECT Two-Syringe-Clip.
 - If the tether strap tears, use the spare joining piece provided in the kit.
 - If a separate joining piece is not available, the system can still be used if care is taken to ensure that the connection is secure and leak-proof.
 - Do NOT expel the air remaining inside the joining piece.
- Attach an application cannula on to the joining piece.
 - Do NOT expel the air remaining inside the joining piece and inside the application cannula until you start the actual application because this may clog the application cannula.

Administration

Prior to applying TISSEEL Lyo the surface of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

- Apply the mixed sealer protein - thrombin solution on to the recipient surface or on to the surfaces of the parts to be glued by slowly pressing on the back of the common plunger.

- In surgical procedures that require the use of minimal volumes of fibrin sealant, it is recommended to expel and discard the first few drops of product.
- After TISSEEL Lyo has been applied, allow at least 2 minutes to achieve sufficient polymerization

Note: If application of the fibrin sealant components is interrupted, clogging may occur in the cannula. In this case, replace the application cannula with a new one immediately before application is resumed. If the openings of the joining piece are clogged, use the spare joining piece provided in the package.

After blending of the sealant components, the fibrin sealant starts to set within seconds due to the high thrombin concentration (500 IU/ml).

The fibrin sealant can also be applied with other accessories supplied by BAXTER which are particularly suited, for example, for endoscopic use, minimally invasive surgery or application to large or difficult-to-access areas. When using these application devices, please follow their instructions for use carefully.

In certain applications, biocompatible material, such as collagen fleece, is used as a carrier substance or for reinforcement.

Spray application

When applying TISSEEL Lyo using a spray device be sure to use a pressure and a distance from tissue within the ranges recommended by the manufacturer as follows:

Recommended pressure, distance and devices for spray application of TISSEEL Lyo					
Surgery	Spray set to be used	Applicator tips to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open wound	Tisseel / Artiss Spray Set	n.a.	EasySpray	10-15cm	1.5-2.0 bar (21.5-28.5 psi).
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		
Laparoscopic/ minimally invasive procedures	n.a.	Duplospray MIS Applicator 20cm	Duplospray MIS Regulator 1.5 bar	2-5 cm	1.2-1.5 bar (18-22 psi)
		Duplospray MIS Applicator 30cm			
		Duplospray MIS Applicator 40cm			
		Spray Set 360 Endoscopic Applicator with Snaplock			
		Spray Set 360 Endoscopic Applicator with Tether			
		Replaceable tip			

When spraying TISSEEL Lyo, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism (see sections 4.2 and 4.4).

For the application of TISSEEL Lyo in enclosed thoracic and abdominal spaces the DuploSpray MIS applicator and regulator system is recommended. Please refer to the instruction manual of the DuploSpray MIS device.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORIZATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]