SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TISSEEL Ready to use

Solutions for Sealant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1:

Sealer Protein Solution

Human Fibrinogen (Clottable Protein)	91 mg[(1)]/ml
Aprotinin (synthetic)	3000 KIU[(2)]/ml

Component 2:

Thrombin Solution

Human Thrombin	500 IU[(3)]/ml
Calcium Chloride Dihydrate	40 µmol/ml

[1] Contained in a total protein concentration of 110.5 mg/ml
[2] 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)
[3] Thrombin activity is calculated using the current WHO International Standard for Thrombin

For excipients, see section 6.1.

1 prefilled double chamber syringe which contains Sealer Protein Solution (with synthetic Aprotinin), deep frozen 1 ml, 2 ml, or 5 ml, in one chamber and Thrombin Solution (with Calcium Chloride Dihydrate), deep frozen 1 ml, 2 ml, or 5 ml, in the other chamber results in 2 ml, 4 ml, or 10 ml total volume of product ready for use.

3 PHARMACEUTICAL FORM

Solutions for Sealant

Colourless to pale yellow and clear to slightly turbid solutions.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment where standard surgical techniques are insufficient

- for improvement of hemostasis (see section 5.1)

- as a tissue glue to promote adhesion/sealing, or as suture support:

    - in gastrointestinal anastomoses

    - in neurosurgery where contact with cerebro-spinal fluid or dura mater may occur

- For mesh fixation in hernia repair, as an alternative or adjunct to sutures or staples.

4.2 Posology and method of administration

TISSEEL is for topical (i.e., epilesional) use only, do not inject.

TISSEEL must not be applied intravascularly (see Section 4.4).

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

Posology

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

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

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 Ready to use should be applied.

If used for tissue adherence, it is recommended that the initial application cover the entire intended application area.

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, 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 Ready to use to a pre-existing polymerized TISSEEL Ready to use layer as TISSEEL Ready to use will not adhere to a polymerized layer.

As a guideline for the gluing of surfaces, 1 pack of TISSEEL Ready to use 2 ml (i.e. 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm^2.

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

When TISSEEL Ready to use is used for mesh fixation it may be applied as drops and/or by a spray technique depending on the preference of the surgeon. Usually the drops of TISSEEL are applied where surgeons routinely position staples and the layer of fibrin sealant achieved with spraying allows the entire mesh to be fixed in place without shrinking and folding.

The quantity of TISSEEL Ready to use required for mesh fixation depends on the mesh size selected and the recommended amount is the same for different application techniques. For example, 2-4 ml of reconstituted TISSEEL Ready to use applied as a thin layer is suitable to adequately fix a standard size mesh of approximately 10 x 15 cm.

When using the drop technique surgeons should apply TISSEEL Ready to use at key anchor points for fixing the mesh (e.g. pubic tubercle in inguinal hernia repair) and at the margins of the mesh. Application by spray, either alone or in combination with drops, should cover the mesh uniformly with a thin layer.

In inguinal hernia repair the mesh covering vascular structures and nerves can be fixed with TISSEEL Ready to use alone using drops and/or spray.

Paediatric population

Safety and efficacy of the product in paediatric patients have not been established.

Method and route of administration

For topical (i.e. epilesional) use only, do not inject.

Prior to application, TISSEEL must be warmed to 33-37°C. Tisseel must not be exposed to temperatures above 37°C and must not be microwaved.

Separate, sequential application of the two components of TISSEEL must be avoided.

In order to ensure optimal safe use of TISSEEL 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 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 must be sprayed only onto application sites that are visible.

TISSEEL 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.

Application beyond the intended area should be avoided.

If application is interrupted, clogging occurs immediately in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the aperture of the joining piece (Y connector) facing the cannula is clogged, use the spare joining piece provided in the package.

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 immediately before application, to ensure use of adequate mixed product (see Section 4.4).

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 application of TISSEEL Ready to use.

After TISSEEL Ready to use has been applied, allow at least 2 minutes to achieve sufficient polymerization. Depending on type of use, the sealed parts may have to be fixed or held in the desired position for this time.

Oxidised cellulose-containing preparations may reduce the efficacy of TISSEEL Ready to use and should not be used as carrier materials (see section 6.2).

It is strongly recommended that every time TISSEEL Ready to use is applied to a 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.

See Section 6.6 for more detailed instructions.

4.3 Contraindications

TISSEEL Ready to use must not be applied intravascularly. Intravascular application of TISSEEL Ready to use may result in life-threatening thromboembolic events.

Known hypersensitivity to any constituents of the product, including aprotinin (see also section 4.4. Warnings).

TISSEEL Ready to use alone is not indicated for the treatment of active or spurting arterial or venous bleeding which is not controlled by conventional surgical techniques.

TISSEEL Ready to use is not indicated to replace skin sutures intended to close surgical wounds.

4.4 Special warnings and precautions for use

TISSEEL Ready to use alone is not indicated for the treatment of severe or brisk arterial or venous bleeding which is not controlled by conventional surgical techniques.

For epilesional use only. Do not apply intravascularly. Soft tissue injection of TISSEEL Ready to use carries the risk of an anaphylactoid reaction and / or local tissue damage.

Caution must be used when applying fibrin sealant using pressurized air or gas. (See Section 4.2 and Section 4.8).

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

Intravascular application can lead to intravascular coagulation and may result in life-threatening thromboembolic events and might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

TISSEEL must be applied with caution to minimize any risk of intravascular application, for example in coronary bypass surgery. Because of the risk of intravascular injection, the product also must not be injected into highly vascularized tissue, such as nasal mucosa.

In two retrospective, non-randomized studies in Coronary Artery Bypass Graft (CABG) surgery, patients that received fibrin sealant showed a statistically significant increased risk of mortality. While these studies could not provide a determination of a causal relationship the increased risk associated with the use of TISSEEL Ready to use in these patients cannot be excluded. Therefore, additional care should be taken to avoid inadvertent intravascular administration of this product.

Injection of Sealer Protein and/or Thrombin Solution carries a risk of anaphylactoid reactions. Intravascular and intraventricular administration carries the additional risk of a thromboembolic complication. Both complications may be life-threatening. Therefore, care should be taken to ensure that Sealer Protein and/or Thrombin Solution are only applied topically.

Caution must be used when applying fibrin sealant using pressurized air or gas

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

Apply TISSEEL 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 CO_2 and therefore cannot be excluded with TISSEEL when sprayed in open wound surgery.

When applying TISSEEL 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 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, 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 (also see section 4.2).

TISSEEL Ready to use must not be used with the EasySpray/Spray set system in enclosed body areas.

Before the administration of TISSEEL Ready to use, 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.

As with any protein containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately.

Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients. Manifestations of hypersensitivity reactions to TISSEEL observed include: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnoea, nausea, urticaria, angioedema, pruritus, erythema, paresthesia. Fatal anaphylactic reactions, including anaphylactic shock, have also been reported with TISSEEL (see section 4.8).

At the first sign or symptom of a hypersensitivity reaction, TISSEEL application must be stopped and medical care initiated. Remaining product must be removed from the site of application.

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

Injecting TISSEEL Ready to use into tissue carries the risk of local tissue damage.

TISSEEL Ready to use contains synthetic aprotinin, a monomeric polypeptide known to be associated with anaphylactic reactions. Even in the case of strict local application of aprotinin there is a risk of anaphylactic reaction, particularly in the case of previous exposure. Aprotinin is included in TISSEEL for its antifibrinolytic properties. As with other aprotinin-containing products, the use of TISSEEL should be documented in the patient's records, pointing out that TISSEEL contains aprotinin.

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

In case of shock, standard medical treatment for shock should be implemented.

If fibrin sealants are applied in confined spaces, the risk of compressive complications should be taken into account.

Sealer Protein Solution and Thrombin Solution are made from human plasma. The risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by inactivating and/or removing 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 or other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

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

It is strongly recommended that every time a patient receives a dose of TISSEEL Ready to use, 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. Oxidised cellulose-containing preparations should not be used with TISSEEL Ready to use (See section 6.2 Incompatibilities).

Adequate data are not available to support the use of this product in application through a flexible endoscope for treatment of bleeding or in vascular surgery.

Safety and effectiveness of the product in pediatric patients has not been established as limited clinical study data are available.

4.5 Interaction with other medicinal products and other forms of interaction

No formal 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.

4.6 Fertility, Pregnancy and lactation

There are no adequate data from the use of TISSEEL Ready to use in pregnant or lactating women.

Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing TISSEEL Ready to use.

No undesirable effects during pregnancy and lactation have been reported.

See section 4.4 for information on Parvovirus B19 infection.

The effects of TISSEEL Ready to use on fertility have not been established.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants / haemostatics.

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 a second treatment with TISSEEL Ready to use was well tolerated, a subsequent administration of TISSEEL or systemic administration of aprotinin may result in severe anaphylactic reactions.

In the event of hypersensitivity reactions the administration has to be discontinued immediately.

Soft tissue injection of TISSEEL Ready to use carries the risk of an anaphylactoid reaction and / or local tissue damage (see Section 4.4).

Reactions to antibodies against components of fibrin sealant / haemostatic products may occur rarely.

Inadvertent intravascular injection could lead to thromboembolic events and disseminated intravascular coagulation, and there is also a risk of anaphylactic reaction (see Section 4.4).

For safety with respect to transmissible agents, see Section 4.4.

The following undesirable effects have been reported from clinical trials investigating the safety and efficacy of TISSEEL and from post-marketing experience with Baxter Fibrin Sealants. In these 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 durasealing in the posterior fossa. In these studies a total of 1146 patients were administered Baxter Fibrin sealant.

For the undesirable effects reported from post-marketing experience with Baxter Fibrin Sealants, the frequency cannot be estimated from the available data.

Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 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*	Not known

	Anaphylactic reactions*	Not known
	Anaphylactic shock*	Not known
	Paresthesia	Not known
	Bronchospasm	Not known
	Wheezing	Not known
	Pruritus	Not known
	Erythema	Not known
Nervous system disorders	Sensory disturbance	Common
Cardiac disorders	Bradycardia	Not known
	Tachycardia	Not known
Vascular disorders	Axillary vein thrombosis **	Common
	Hypotension	Rare
	Haematoma (NOS)	Not known
	Embolism arterial	Not known
	Air embolism***	Not known
	Cerebral artery embolism	Not known
	Cerebral infarction**	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known
Gastrointestinal disorders	Nausea	Uncommon
	Intestinal obstruction	Not known
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria	Not known
	Impaired healing	Not known
Musculoskeletal and connective tissue disorders	Pain in an extremity	Common
General disorders and administration site conditions	Procedural pain	Uncommon
	Pain	Common
	Increased body temperature	Common
	Flushing	Not known
	Oedema	Not known
Injury, poisoning and procedural complications	Seroma	Very common
	Angioedema	Not known

***** 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.

Class Reactions

Other adverse reactions associated with the fibrin sealant/hemostatic class include: Air or gas embolism when using devices with pressurized air or gas; this event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface. 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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: V03A K

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 Ready to use as an antifibrinolytic to prevent premature degradation of the clot.

Efficacy in haemostasis has been demonstrated in cardiopulmonary surgery, splenic surgery and neurosurgery.

Use as tissue glue to promote adhesion/sealing or as suture support: Efficacy has been demonstrated in surgeries including gastrointestinal anastomoses and neurosurgical procedures where contact with cerebro-spinal fluid or dura mater can occur.

Clinical studies demonstrating haemostasis, sealing, and tissue adhesion were conducted in at least 4,706 patients. These studies were performed in a multitude of surgical specialties, surgical procedures and applications techniques, including but not limited to haemostasis (n=1300), gastrointestinal anastomoses (n=1,114), neurosurgery (n=511).

21 open and comparative clinical studies have also been conducted in 2625 patients to demonstrate the use of TISSEEL in mesh fixation during inguinal, femoral and incisional

hernia repair by various open and laparoscopic techniques. TISSEEL was at least as effective as staples, tacks or sutures in mesh fixation during the repair of inguinal or femoral hernia using all the currently favoured surgical techniques. TISSEEL was at least as effective in repair of incisional hernias when judged by recurrence rates. In addition, the evidence demonstrated that there were no differences in postoperative complications between mesh fixation methods. In several studies the level of postoperative pain was significantly lower in the TISSEEL group.

There is limited experience in children during cardiac surgery (age 4-134 months: n=14).

Fibrin Sealant VH S/D (frozen presentation) was evaluated in a prospective, parallel design, randomized (1:1), double-blind, multicenter clinical study against a previous single virus inactivated formulation of the product, Fibrin Sealant VH (lyophilized presentation), in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) and median sternotomy. Patients were treated with Fibrin Sealant VH S/D 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, Fibrin Sealant VH S/D 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.

Hemostasis within 5 minutes and maintained until surgical closure		
	FIBRIN SEALANT VH S/D	FIBRIN SEALANT VH
Intent to Treat Analysis	127/144 (88.2%)	129/144 (89.6%)
Per Protocol Analysis	108/123 (87.8%)	122/135 (90.4%)

No difference to control groups not receiving Fibrin Sealant VH S/D was observed in an exploratory study in hip joint replacement for postoperative blood loss and in a study in axillary lymph node dissection for duration of axillary drainage.

5.2 Pharmacokinetic properties

Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

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

5.3 Preclinical safety data

No preclinical safety data are available for Fibrin Sealant VH S/D on subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation.

Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of Fibrin Sealant VH S/D (frozen presentation). There was no evidence of mutagenicity in appropriate *in vitro* tests.

Fibrin Sealant VH S/D (frozen presentation) was well tolerated in wound healing models in rats and rabbits.

The Sealer Protein Solutions of Fibrin Sealant VH S/D (frozen and lyophilized presentations) were also well tolerated by *in vitro* human fibroblast cultures demonstrating cellular compatibility and non-cytotoxicity.

Based on a detailed literature review, toxicity of the residual solvent/detergent reagents (see 6.1) on Fibrin Sealant VH S/D can be essentially excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component 1: Sealer Protein Solution

Human Albumin
L-Histidine
Niacinamide
Polysorbate 80 (Tween 80)
Sodium Citrate Dihydrate
Water for Injections

Component 2: Thrombin Solution

Human Albumin
Sodium Chloride
Water for Injections

6.2 Incompatibilities

Sealer Protein and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals. TISSEEL must not be mixed with other medicinal products.

6.3 Shelf life

TISSEEL Ready to use has a shelf life of two years. The expiry date is stated on the package.

Shelf life for thawed product see section 6.6.

6.4 Special precautions for storage

Keep out of the reach and sight of children.

AST Syringe: Store in a freezer (at ≤-18°C).

PRIMA Syringe: Store in a freezer (at ≤-20°C).

The cold storage chain must not be interrupted until use.

Keep TISSEEL Ready to use in the outer carton to protect from light.

The unopened product, thawed at up to 25°C, may be stored at not more than 25°C for up to 72 hours. If the solution is not used within 72 hours after thawing, dispose of TISSEEL

Do not refreeze or refrigerate after thawing.

6.5 Nature and contents of container

Content of package with PRIMA Syringe:

- 1 ml, 2 ml or 5 ml sealer protein solution and 1 ml, 2 ml or 5 ml thrombin solution in a pre-filled double chamber syringe (polypropylene) closed with a tip cap packed in two bags and with a device with 2 joining pieces and 4 applications cannulas.

Or

Content of package with AST Syringe:

1 ml, 2 ml or 5 ml sealer protein solution and 1 ml, 2 ml or 5 ml thrombin solution in a pre-filled double chamber syringe (polypropylene) closed with a tip cap packed in two bags and with a device with 2 joining pieces, 4 applications cannulas and one double piston plunger.

1) One chamber contains: Component 1 - Sealer Protein Solution

Active substances: Human Fibrinogen (Clottable Protein) 72 – 110 mg/ml, Aprotinin (synthetic) 3000 KIU/ml

2) One chamber contains: Component 2 - Thrombin Solution

Active substances: Human Thrombin 500 IU/ml, Calcium Chloride Dihydrate 40 µmol/ml

TISSEEL Ready to use is available in the following pack sizes:

- TISSEEL Ready to use 2 ml
  (containing 1 ml of Sealer Protein Solution and 1 ml of Thrombin Solution)
- TISSEEL Ready to use 4 ml
  (containing 2 ml of Sealer Protein Solution and 2 ml of Thrombin Solution)
- TISSEEL Ready to use 10 ml
  (containing 5 ml of Sealer Protein Solution and 5 ml of Thrombin Solution)

Not all pack sizes may be marketed.

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

6.6 Special precautions for disposal

General

Before administration of TISSEEL Ready to use care has to be taken that parts of the body outside the desired application area are sufficiently covered to prevent tissue adhesion at undesired sites.

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

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

Do NOT thaw the product by holding it in your hands.

Handling and Preparation

Both the Sealer Protein Solution and the Thrombin Solution are contained in a single-use double-chamber syringe. The nozzles of the pre-filled double-chamber syringe are closed by one tip cap and each barrel of the syringe is closed by a silicone rubber stopper. The entire assembly is packed and hermetically sealed in two sterilized aluminum-plastic-compound bags under aseptic conditions. The inner bag and its contents are sterile unless the integrity of the outside package is compromised. Using sterile technique, transfer the sterile inner pouch and contents onto the sterile field.

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. (In order to control the specified temperature range, the water temperature should be monitored using a thermometer and the water should be changed as necessary. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum-plastic bags.)

The protective syringe cap should not be removed until thawing is complete and application tip is ready to be attached. For PRIMA syringe: To facilitate removal of the tip cap from the syringe, rock the tip cap by moving it backward and forward, then pull the protective cap off the syringe.

Do not use TISSEEL Ready to use unless it is completely thawed and warmed to 33°C – 37°C (liquid consistency).

Thawing/warming PRIMA Syringe

The PRIMA syringe may be thawed AND warmed using one of the following methods:

1. **Rapid thawing/warming (sterile water bath) – *Recommended method***
2. Thawing/warming in a non-sterile water bath
3. Thawing/warming in an incubator
4. The ready-to-use syringe may also be thawed and kept at room temperature (not above 25°C) for up to 72 hours. Warming is required prior to use.

1) Rapid thawing/warming (sterile water bath) – *Recommended method*

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C.

- The water bath must not exceed a temperature of 37°C. In order to monitor the specified temperature range, control the water temperature using a thermometer and change the water as necessary.
- When using a sterile water bath for thawing and warming, remove the pre-filled syringe from the bags before placing it in the sterile water bath.

Instructions:

Bring the inner bag into the sterile area, remove the ready-to-use syringe from the inner bag and place it directly in the sterile water bath. Ensure that the content of the ready-to-use syringe is completely immersed in the water.

Table 1: Minimum thawing and warming times using a sterile water bath

Pack Size	Minimum Thawing/Warming Times 33°C to 37°C, Sterile Water Bath Product without bags
2 ml	5 minutes
4 ml	5 minutes
10 ml	10 minutes

2) Thawing/warming in a non-sterile water bath

Instructions:

Leave the ready-to-use syringe inside both bags and place it in a water bath outside the sterile area for the appropriate length of time (see Table 2). Ensure that the bags remain

immersed in the water during the entire thawing time. After thawing, remove the bags from the water bath, dry the outer bag and bring the inner bag with the ready-to-use syringe into the sterile area.

Table 2: Minimum thawing and warming times using a non-sterile water bath

Pack Size	Minimum Thawing/Warming Times 33°C to 37°C, Non-sterile Water Bath Product in bags
2 ml	15 minutes
4 ml	20 minutes
10 ml	35 minutes

3) Thawing/warming in an incubator

Instructions:

Leave the ready-to-use syringe inside both bags and place it in an incubator outside the sterile area for the appropriate length of time (see Table 3). After thawing/warming, remove the bags from the incubator, remove the outer bag and bring the inner bag with the ready-to-use syringe into the sterile area.

Table 3: Minimum thawing and warming times in an incubator

Pack Size	Minimum Thawing/Warming Times 33°C to 37°C, Incubator Product in bags
2 ml	40 minutes
4 ml	50 minutes
10 ml	90 minutes

4) Thawing at room temperature (not above 25°C) BEFORE warming

Instructions:

Leave the ready-to-use syringe inside both bags and thaw it at room temperature outside the sterile area for the appropriate length of time (see Table 4). Once thawed, in order to warm the product for use, warm it in the outer bag in an incubator.

Table 4: Minimum thawing times at room temperature outside of the sterile field and additional warming times in an incubator to 33°C to 37°C

Pack Size	Minimum Thawing Times of product at room temperature (not above 25°C) followed by additional warming, prior to use, in an incubator at 33°C to a maximum of 37°C Product in bags	
	Minimum Thawing/Warming Times 33°C to 37°C, Incubator Product in bags	Warming in Incubator (33-37°C)
2 ml	80 minutes	+11 minutes
4 ml	90 minutes	+13 minutes
10 ml	160 minutes	+25 minutes

Thawing/warming AST Syringe

The AST syringe may be thawed AND warmed using one of the following methods:

The thawing and warming times when using a sterile water bath are indicated in Table 1 below.

Table 1: Thawing and Warming Times with Sterile Water Bath at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times (Product Removed from aluminum-plastic bags)
2 ml	5 minutes
4 ml	5 minutes
10 ml	12 minutes

Alternatively, the sealant components may be thawed and warmed in an incubator between 33°C and 37°C. The thawing and warming times in the incubator are indicated in Table 2 below. The times refer to product in the aluminum-plastic bags.

Table 2: Thawing and Warming Times in Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times in Incubator (product in aluminum-plastic bags)
2 ml	40 minutes
4 ml	85 minutes
10 ml	105 minutes

A third alternative is to thaw the product at room temperature. Times given in Table 3 are minimum times for thawing at room temperature. The maximum time the product can be kept (in both aluminum-plastic bags) at room temperature is 72 hours.

When thawing at room temperature, the product must be additionally warmed to 33°C – 37°C in an incubator just before use. Respective thawing times in the incubator are also given in Table 3.

Table 3. Thawing and warming times at Room Temperature (=RT) followed by an additional warming, prior to use, in Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing Times at Room Temperature (product in aluminum-plastic bags)		Warming Times at 33-37°C in Incubator after Thawing at RT (product in aluminum-plastic bags)
2 ml	60 minutes	+	15 minutes
4 ml	110 minutes	+	25 minutes
10 ml	160 minutes	+	35 minutes

Stability after thawing

After **thawing and warming** (at temperatures between 33°C and 37°C, water bath or incubator methods), chemical and physical product stability has been demonstrated for 12 hours at 33°C to 37°C.

For product **thawed** at room temperature in the unopened bag, chemical and physical product stability has been demonstrated for 72 hours at temperatures no more than 25°C. Warm to 33°C to 37°C immediately before use. If not used within 72 hours after thawing, TISSEEL Ready to use has to be discarded.

From a microbiological point of view, unless the method of opening/thawing precludes the risks of microbial contamination, the product should be used immediately after being warmed to 33°C to 37°C.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Do not re-freeze or refrigerate once thawing has been initiated.

Handling after thawing / before application

To facilitate optimal blending of the two solutions, the two sealant components must be warmed to 33 – 37°C immediately before use. (The temperature of 37°C must, however, not be exceeded!)

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Before use, check the thawed product visually for particles, discoloration or other changes in its appearance. If one of the above occurs, dispose of the solutions.

The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (e.g., due to an interruption of the cold storage chain or by overheating during warming). In this case, the TISSEEL Ready to use must not be used.

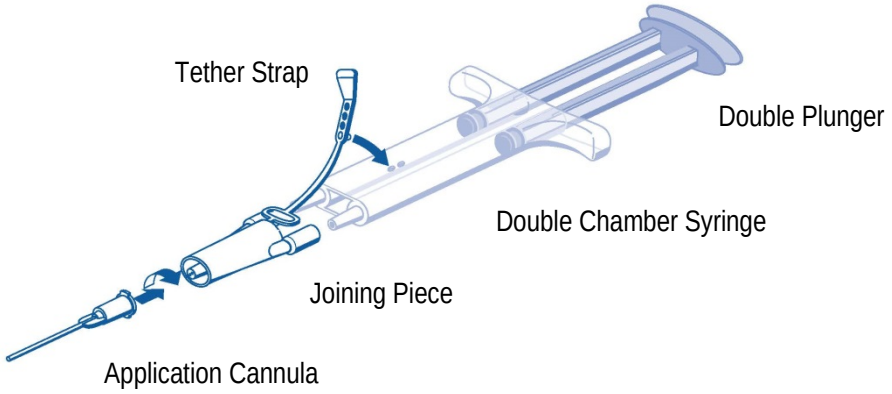
- Remove the syringe from the bags shortly before use.
- Use TISSEEL only when it is thawed and warmed completely (liquid consistency).
- Remove the protective cap from the syringe immediately before application.
  For PRIMA syringe: To facilitate removal of the tip cap from the syringe, rock the tip cap by moving it backward and forward, then pull the protective cap off the syringe.

For further preparation instructions please refer to the responsible nurse or medical doctor.

Administration with PRIMA Syringe:

For application, connect the double chamber ready-to-use syringe with the sealer protein solution and the thrombin solution to a joining piece and an application cannula – both are provided in the set with the application devices. The common plunger of the double chamber ready-to-use syringe 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 for PRIMA Syringe:



- 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 hole.
- Connect the nozzles of the double chamber ready-to-use syringe to the joining piece, ensuring that they are firmly attached.
    - Secure the joining piece by fastening the tether strap to the double chamber ready-to-use syringe.
    - If the tether strap tears, use the spare joining piece provided in the kit.
    - If a spare 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

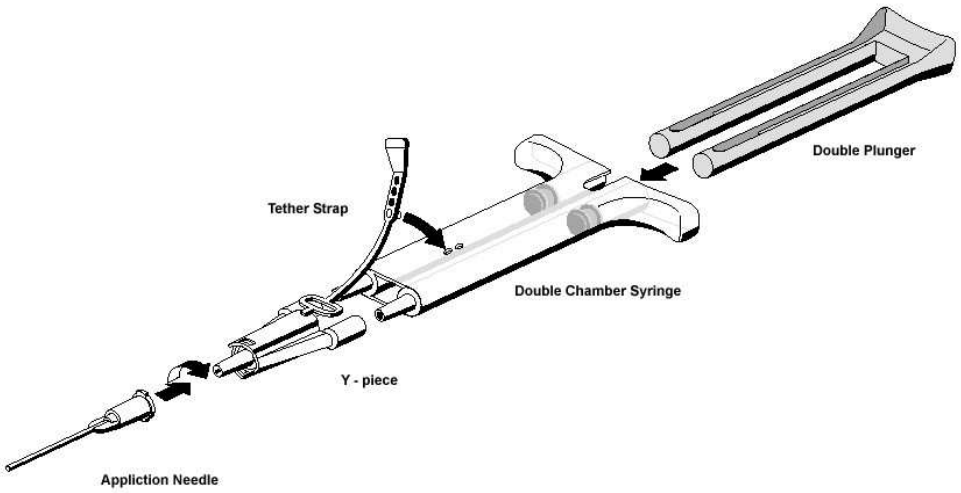
Prior to applying TISSEEL the surface of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

- 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 has been applied, allow at least 2 minutes to achieve sufficient polymerization

Administration with AST Syringe

For application, the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution has to be connected to a joining piece and an application needle as provided in the accompanying set of devices. The common plunger of the double-chamber

syringe ensures that equal volumes are fed through the joining piece before being mixed in the application needle and ejected.



- Connect the nozzles of the double-chamber syringe to the joining piece ensuring that they are firmly fixed. Secure the joining piece by fastening the tether strap to the double-chamber syringe. If the pull strap tears, use the spare joining piece. If none is available, further use is still possible but tightness of the connection needs to be ensured to prevent any risk of leaking.

- Fit an application needle onto the joining piece.

- Do not expel the air remaining inside the joining piece or application needle until you start actual application as the aperture of the needle may clog otherwise.

- Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

- For surgical procedures that require minimal volumes of fibrin sealant do not use the first few drops of TISSEEL Ready to use (see sections 4.2 and 4.4).

If application of the fibrin sealant components is interrupted, clogging occurs immediately in the needle. Replace the application needle with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

Note: After blending of the sealant components, the fibrin sealant starts to set within seconds on account of the high Thrombin concentration (500 IU/ml).

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g. endoscopic use, minimally invasive surgery, application to large or difficult-to-access areas. When using these application devices, strictly follow the Instructions for Use of the devices.

After the two components have been applied, approximate the wound areas. Fix or hold the glued parts with continuous gentle pressure in the desired position to ensure that the

setting fibrin sealant adheres firmly to the surrounding tissue. Allow at least 2 minutes to achieve sufficient polymerization.

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

Spray application

When applying TISSEEL 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					
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	10-15 cm	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 Snap Lock			
		Spray Set 360 Endoscopic Applicator with Tether			
		Replaceable tip			

When spraying the 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 (see sections 4.2 and 4.4).

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford
Norfolk
IP24 3SE
UK

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