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 (as clottable Protein)	91 mg[1]/ml
Human Factor XIII	0.6 - 5 IU/ml
Aprotinin	3000 KIU[2]/ml

Component 2:
Thrombin Solution

Human Thrombin	500 IU[3]/ml
Calcium Chloride	40 micromoles/ml

For a full list of excipients, see section 6.1.

1 prefilled double chamber syringe which contains Sealer Protein Solution (with Aprotinin), deep frozen 1 ml, 2 ml, or 5 ml, in one chamber and Thrombin Solution (with Calcium Chloride), 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

As a coagulant producer for use as a tissue sealant and haemostatic, for surgical incisions, plastic surgical repairs, orthopaedic, traumatic, and dental surgery.

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 4.3)

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

---

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.

Posology:

The amount of TISSEEL 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, 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.

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

As a guideline for the gluing of surfaces, 1 pack of TISSEEL 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 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.

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

The user must follow the instructions and precautions in the device user manual, for example regarding the need to limit the gas pressure in accordance with the instructions, and is cautioned against the spray application of TISSEEL with devices produced by other manufacturers (see also section 4.4).

The only device designed for the application of TISSEEL in enclosed thoracic and abdominal spaces is the DuploSpray MIS applicator and regulator system. However, all the other instructions and warnings listed in the previous paragraph and in section 4.4 still apply.

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 the mixed Sealer Protein - Thrombin Solutions, or of the individual components, should be applied.

Excessive thickness of the fibrin layer may negatively interfere with the product's efficacy and the wound healing process.

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

In cases where very small volumes (1 to 2 drops) of TISSEEL are administered, expel and discard the first several drops from the application cannula immediately before application, to ensure use of adequate mixed product (see section 4.4)

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.

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.

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.

If the aperture of the joining piece (Y connector) facing the cannula is clogged, use the spare joining piece provided in the package.

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.

Oxidised cellulose containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials (see Section 6.2).

After TISSEEL 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.

It is strongly recommended that every time TISSEEL 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.

4.3 Contraindications

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

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

TISSEEL must not be used to replace skin sutures intended to close surgical wounds.

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

4.4 Special warnings and precautions for use

Caution must be used when applying fibrin sealant using pressurized air or gas (See Section 4.2 and Section 4.8.2).

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

Soft tissue injection of TISSEEL carries the risk of local tissue damage.

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. 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 in these patients cannot be excluded. Therefore, additional care should be taken to avoid inadvertent intravascular administration of this product.

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

The product also must not be injected into highly vascularized tissue, such as nasal mucosa.

In surgical applications that require the use of minimal volumes of fibrin sealant (e.g. pterygium surgery) the first few drops should be expelled and discarded before application to ensure adequate mixing of the sealer protein and thrombin solutions.

Use of the first few drops in these procedures could result in the product being ineffective.

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 must not be used with the EasySpray/Spray set in enclosed body areas

Injection into the nasal mucosa must be avoided as thromboembolic complications may occur in the ophthalmic arterial region.

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

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. Manifestations of hypersensitivity reactions to TISSEEL observed include: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnea, 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.

TISSEEL contains a synthetic protein (aprotinin) a polypeptide known to be associated with anaphylactic reactions. 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.

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.

In the event of anaphylactic or severe hypersensitivity reactions, administration is to be discontinued and state-of-the-art emergency measures are to be taken.

Because this product is made from human plasma, a risk of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. 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 (fetal infection) and for individuals with immunodeficiency or increased red blood cell turnover (e.g. hemolytic anemia).

It is strongly recommended that every time a patient receives a dose of TISSEEL, the name and batch number of the product are recorded in order to maintain a record of the batches used.

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

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 in pregnant or lactating women.

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

No undesirable effects during pregnancy and lactation have been reported.

See section 4.4 for information on Parvovirus B19 infection.

The effects of TISSEEL 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 but are not limited to angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnea, 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/hemostatics.

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 was well tolerated, a subsequent administration of TISSEEL or systemic administration of aprotinin may result in severe anaphylactic reactions.

Antibodies against components of fibrin sealant/hemostatic may rarely occur.

VASCULAR DISORDERS: Embolism arterial, including cerebral artery embolism, cerebral infarction*

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Impaired healing

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

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 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.

The following ADRs have been reported from three clinical trials on TISSEEL and from post-marketing experience with Baxter Fibrin Sealants.

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
	Cerebral artery embolism	Not known
	Cerebral infarction**	Not known
	Air embolism***	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. mailto: Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, Dublin 2, Ireland; Tel: +353 1 676 4971; Fax: +353 1 676 2517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics, ATC code: B02BC; 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 as an antifibrinolytic to prevent premature degradation of the clot.

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 (frozen presentation) 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

For efficacy, *in vivo* studies in four animal models closely imitating the situation in patients were used. Fibrin Sealant VH S/D (frozen and lyophilized presentations) demonstrated efficacy regarding primary, secondary and sustained hemostasis and sealing.

Due to its nature as well as its method of application and mechanism of action (usually single, only in exceptional cases repeated application of small volumes; local efficacy without systemic exposure or distribution to other organs and tissues), 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). Furthermore, no evidence for mutagenicity could be seen in appropriate *in vitro* tests.

Fibrin Sealant VH S/D (frozen presentation) proved 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 excellent cellular compatibility and non-cytotoxicity. Based on a detailed literature review, any negative influence or 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 Solution
Histidine
Nicotinic Acid
Polysorbate 80 (Tween 80)
Sodium Citrate
Water for Injections

Component 2: Thrombin Solution
Human Albumin Solution
Sodium Chloride
Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.
Thawed, unopened pouches may be stored for up to 72 hours at room temperature (up to +25°C).

6.4 Special precautions for storage

Store and transport frozen (at ≤ -20°C). Keep out of the reach and sight of children.
Keep the syringe in the outer carton in order to protect from light.
Thawed, unopened pouches may be stored for up to 72 hours at controlled room temperature (not exceeding +25°C) after thawing.

If not used within 72 hours after thawing, TISSEEL has to be discarded.

Once thawed, TISSEEL must not be refrozen or refrigerated (the sealer protein component forms a gel at refrigerator temperature).

6.5 Nature and contents of container

TISSEEL 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).

Not all pack sizes may be marketed.

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 of sealer protein solution and 1, 2 or 5 ml of Thrombin Solution in a single-use double-chamber syringe (polypropylene) with a tip-cap sealed in two sterilized aluminium-plastic bags. One set of application devices (DUO - Set: 2 joining pieces, 4 application cannulas (blunt), 1 Double syringe plunger)

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

6.6 Special precautions for disposal and other handling

General
Before administration of TISSEEL 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 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 aluminium-plastic 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 aluminium-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 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:

Thawing option 1 - sterile water bath:

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 aluminium-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 aluminium-plastic bags.

Thawing option 2 – incubator:

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 aluminium-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 aluminium-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.

Thawing option 3 - room temperature:

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

Stability after thawing

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.

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 in the PRIMA Syringe.

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.

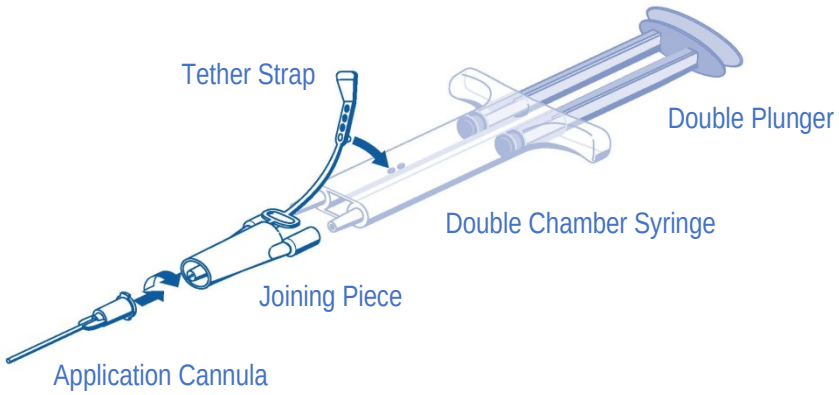
The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (e.g., due to an interruption of the cold storage chain or by overheating during warming). In this case, the TISSEEL must not be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

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.

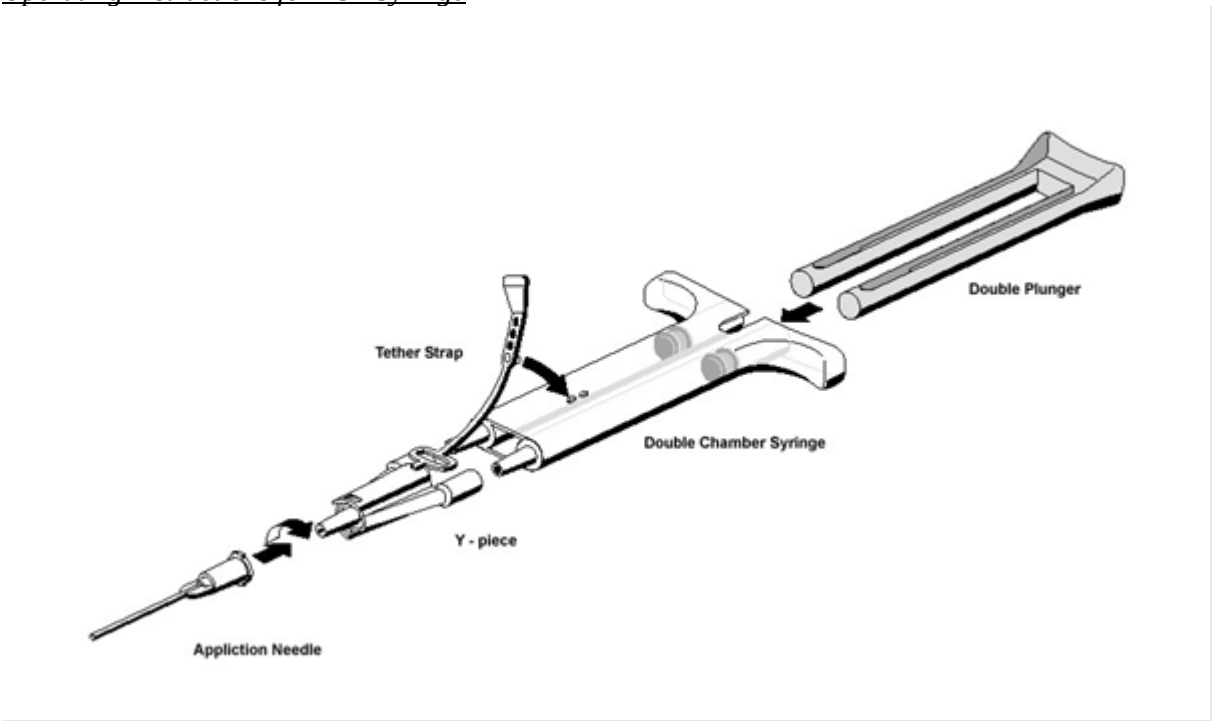
- Apply the mixed sealer protein - thrombin solution on to the recipient surface or on to the surfaces of the parts to be glued by slowly pressing on the back of the common plunger.
- In surgical procedures that require the use of minimal volumes of fibrin sealant, it is recommended to expel and discard the first few drops of product.
- After TISSEEL has been applied, allow at least 2 minutes to achieve sufficient polymerization

Or

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 cannula 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 cannula and ejected.

Operating Instructions for AST Syringe



- 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 cannula onto the joining piece.
- Do not expel the air remaining inside the joining piece or application cannula until you start actual application as the aperture of the cannula may clog otherwise.
- Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

  If application of the fibrin sealant components is interrupted, clogging occurs immediately in the cannula. Replace the application cannula 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 for about 3–5 minutes to ensure that the setting fibrin sealant adheres firmly to the surrounding tissue.

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:

<table>
<tr><th colspan="6">Recommended pressure, distance and devices for spray application of TISSEEL</th></tr>
<tr><th>Surgery</th><th>Spray set to be used</th><th>Applicator tips to be used</th><th>Pressure regulator to be used</th><th>Recommended distance from target tissue</th><th>Recommended spray pressure</th></tr>
<tr><td rowspan="2">Open wound</td><td>TISSEEL / Artiss Spray Set</td><td>n.a.</td><td>EasySpray</td><td rowspan="2">10-15cm</td><td rowspan="2">1.5-2.0 bar (21.5-28.5 psi).</td></tr>
<tr><td>TISSEEL / Artiss Spray Set 10 pack</td><td>n.a.</td><td>EasySpray</td></tr>
<tr><td rowspan="8">Laparoscopic/ minimally invasive procedures</td><td rowspan="8">n.a.</td><td rowspan="2">Duplospray MIS Applicator 20cm</td><td>Duplospray MIS Regulator</td><td rowspan="8">2 – 5 cm</td><td rowspan="8">1.2-1.5 bar (18-22 psi)</td></tr>
<tr><td>Duplospray MIS Regulator NIST B11</td></tr>
<tr><td rowspan="2">Duplospray MIS Applicator 30cm</td><td>Duplospray MIS Regulator</td></tr>
<tr><td>Duplospray MIS Regulator NIST B11</td></tr>
<tr><td rowspan="2">Duplospray MIS Applicator 40cm</td><td>Duplospray MIS Regulator</td></tr>
<tr><td>Duplospray MIS Regulator NIST B11</td></tr>
<tr><td rowspan="2">Replaceable tip</td><td>Duplospray MIS Regulator</td></tr>
<tr><td>Duplospray MIS Regulator NIST B11</td></tr>
</table>

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 Holding B.V.
Kobaltweg 49,
3542CE Utrecht,
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

PA2299/025/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th November 2010
Date of last renewal: 18th November 2015

10. DATE OF REVISION OF THE TEXT

July 2020