TISSEEL FROZEN
Solutions for sealant

PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

TISSEEL FROZEN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1: Sealer protein solution

Human fibrinogen (as clottable protein)	91 mg[1]/ml
Aprotininacetate	3000 KIU[2]/ml

Excipient(s) with known effect:

Polysorbate 80	1.25 mg/ml

Component 2: Thrombin solution

Human thrombin	500 IU[3]/ml
Calcium chloride dihydrate	40 μmol/ml

1, 2 or 5 ml sealer protein solution (with synthetic aprotinin) and 1, 2 or 5 ml thrombin solution (with calcium chloride dihydrate) combine to make 2, 4 or 10 ml ready-to-use fibrin sealant 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

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.

TISSEEL FROZEN 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.

3. PHARMACEUTICAL FORM

Solutions for sealant

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment in adults and children from 1 month of age where standard surgical techniques appear insufficient:

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

Posology

The amount of TISSEEL FROZEN 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 FROZEN to a pre-existing polymerized TISSEEL FROZEN layer as TISSEEL FROZEN will not adhere to a polymerized layer.

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

When TISSEEL FROZEN 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 FROZEN should be applied.

Method of administration

For epilesional use.

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

TISSEEL FROZEN 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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

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

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

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 FROZEN 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 FROZEN when sprayed in open wound surgery.

When applying TISSEEL FROZEN 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 FROZEN 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 FROZEN, 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 FROZEN must not be used with the Easy Spray / Spray Set system in enclosed body areas.

Before the administration of TISSEEL FROZEN, 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 FROZEN. 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 FROZEN 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 FROZEN 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 FROZEN 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 FROZEN into tissue carries the risk of local tissue damage.

TISSEEL FROZEN 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 FROZEN 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 FROZEN (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 FROZEN was well tolerated, a subsequent administration of TISSEEL FROZEN 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 FROZEN and from post-marketing experience (marked with a ^{p} in the adverse event table below) with Baxter Fibrin Sealants. In the clinical trials, TISSEEL FROZEN 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 FROZEN in the clinical trials from which data were included in the SmPC)

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* [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 complications	Procedural pain	Uncommon
	Seroma	Very common
	Angioedema [p]	Uncommon

***** 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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 FROZEN 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 FROZEN 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 FROZEN, 93 with control) undergoing vascular surgery with ePTFE conduits, in a total of 70 patients (35 with TISSEEL FROZEN, 35 with control) undergoing partial hepatic resection and in a total of 317 patients (157 with TISSEEL FROZEN, 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 FROZEN 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 FROZEN, 59 with control).

5.2 Pharmacokinetic properties

TISSEEL FROZEN 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 FROZEN 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 FROZEN. 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 FROZEN can be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component 1: Sealer protein solution:

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

Component 2: Thrombin solution:

Protein (by addition of human albumin)
Sodium chloride
Water for Injections

6.2 Incompatibilities

Oxidized cellulose-containing preparations should not be used with TISSEEL FROZEN 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

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below -20°C. Store in the original package in order to protect from light.

After thawing: after **thawing and warming** (at temperatures between 33°C and 37°C), chemical and physical product stability has been demonstrated for 12 hours at 33°C to 37°C.
For product **thawed** at up to 25°C in the unopened bag, chemical and physical product stability has been demonstrated for 72 hours at temperatures not more than 25°C.
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 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.

Or

Content of package with Duo Syringe System:

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

Pack sizes:
TISSEEL FROZEN 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.

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

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

- The guideline for sealing surfaces is: One package of TISSEEL FROZEN 2 ml (i.e. 1 ml sealer protein solution plus 1 ml thrombin solution) is sufficient for a surface of at least 10 cm^2.

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

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

- Do NOT expose TISSEEL FROZEN to temperatures above 37°C. Do NOT microwave.
- Do NOT thaw the product by holding it in your hands.
- Do NOT use TISSEEL FROZEN until it is completely thawed and warmed to 33°C – 37°C.
- Remove the protective cap of the syringe only when thawing and warming is complete.
  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.

- Expel all air from the syringe then attach the joining piece and application cannula.

Instructions for handling and preparation:
Both the sealer protein solution and the thrombin solution are contained in a ready-to-use syringe. The product is packed in two sterile bags under aseptic conditions. The inner bag and its contents are sterile as long as the outer bag remains intact. Using sterile technique, transfer the sterile inner pouch and contents onto the sterile field.

The ready-to-use 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		
	PRIMA Syringe	**AST Syringe**	**Duo Syringe System**
2 ml	5 minutes	5 minutes	8 minutes
4 ml	5 minutes	5 minutes	9 minutes
10 ml	10 minutes	12 minutes	13 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		
	PRIMA Syringe	**AST Syringe**	**Duo Syringe System**
2 ml	15 minutes	30 minutes	31 minutes
4 ml	20 minutes	40 minutes	46 minutes
10 ml	35 minutes	80 minutes	64 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		
	PRIMA Syringe	**AST Syringe**	**Duo Syringe System**

2 ml	40 minutes	40 minutes	62 minutes
4 ml	50 minutes	85 minutes	77 minutes
10 ml	90 minutes	105 minutes	114 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**					
	PRIMA Syringe		**AST Syringe**		**Duo Syringe System**	
	Thawing at room temperature (not above 25°C)	**Warming in Incubator (33-37°C)**	**Thawing at room temperature (not above 25°C)**	**Warming in Incubator (33-37°C)**	**Thawing at room temperature (not above 25°C)**	**Warming in Incubator (33-37°C)**
2 ml	80 minutes	+11 minutes	60 minutes	+15 minutes	82 minutes	+28 minutes
4 ml	90 minutes	+13 minutes	110 minutes	+25 minutes	117 minutes	+30 minutes
10 ml	160 minutes	+25 minutes	160 minutes	+35 minutes	167 minutes	+44 minutes

After thawing at room temperature, the product must be used within 72 hours of removing from the freezer.

Stability after thawing
After **thawing and warming** (at temperatures between 33°C and 37°C, methods 1, 2 and 3), 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 (method 4), 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.

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 achieve optimal blending of the two solutions and optimal solidification of the fibrin sealant, **maintain the two sealant components at 33°C - 37°C until application.**

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.

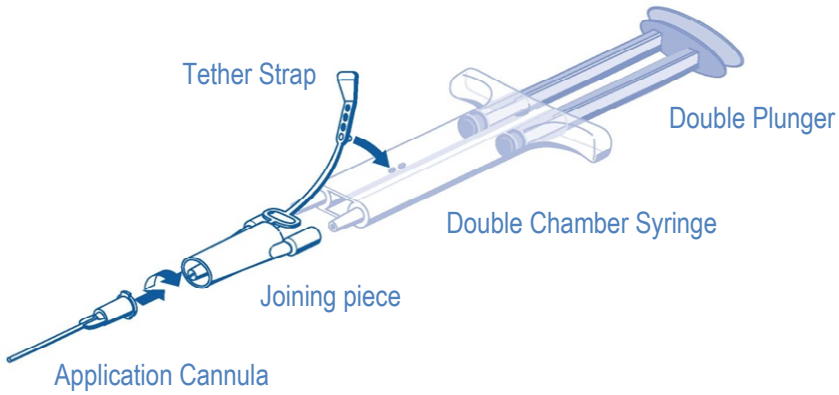
The thawed sealer protein solution should be liquid but slightly viscous. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (possibly due to an interruption of the cold storage chain or by overheating during warming). In this case, do NOT use TISSEEL FROZEN on any account.

- Remove the syringe from the bags shortly before use.
- Use TISSEEL FROZEN 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

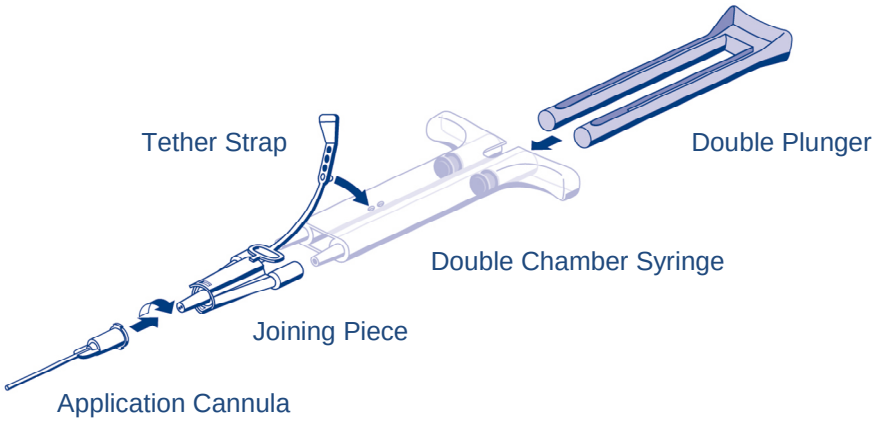
Prior to applying TISSEEL FROZEN the surface of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

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

Or

Administration with AST 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, likewise provided in the set with the application devices, 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 AST 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.

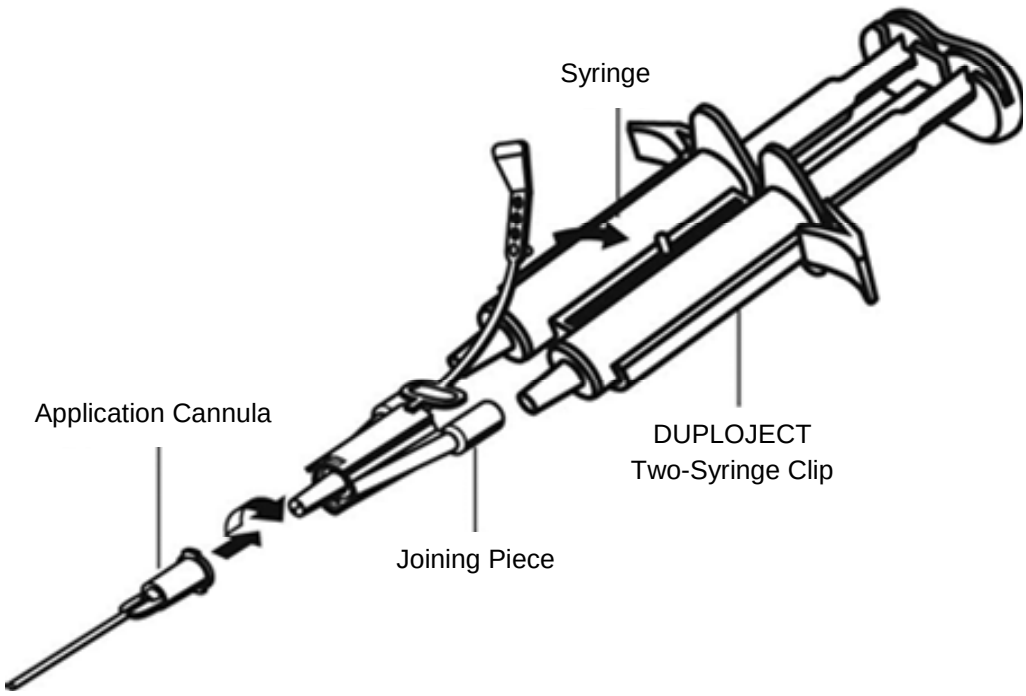
Administration
Prior to applying TISSEEL FROZEN the surface of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Do not use pressurized air or gas for drying the site.

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

Or

Administration with Duo Syringe System:
For application, connect the two single use syringes with the sealer protein solution and with the thrombin solution to a joining piece and an application cannula as provided in the accompanying Set of Devices (DUPLOJECT COMBI). The common plunger of the DUPLOJECT Two-Syringe Clip ensures that equal volumes are fed through the joining piece into the application cannula where they are blended and then applied.

Operating instructions for Duo Syringe System:



- 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 the Duo Syringe System 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 FROZEN 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 FROZEN 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 FROZEN 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 FROZEN					
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 TISSEEL FROZEN, 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).

For the application of TISSEEL FROZEN 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. REGISTRATION NUMBER

162-87-35322

8. MANUFACTURER

Baxter AG, Vienna, Austria

9. REGISTRATION HOLDER

Baxter Healthcare Distribution Ltd., 34 Jerusalem St., Ra'anana, Israel.

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in October 2019