14th February 2022

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

Tisseel Ready to use Solutions for Sealant:
Supply of batches with incomplete package leaflet technical information section

Dear Healthcare Professional,

To ensure continuity in supply, Baxter Healthcare Limited has obtained approval from the Medicines and Healthcare products Regulatory Agency (MHRA) to supply 3 batches of Tisseel Ready to use, solutions for sealant with incomplete text within the technical information section of the package leaflet.

Summary:

- **The 3 affected batches contain package leaflets with incomplete text in the technical information section intended for healthcare professionals**
- **The incorrect package leaflet sections contain a previously approved version of the text and do not contain the current instructions for use and disposal, handling, preparation and administration sections – see page 2 for full details**
- **The section of the package leaflet intended for patients is correct and complete**
- **There is no risk to product quality as a result of this issue**
- **Healthcare professionals are advised to exercise caution when using this product and to refer to the correct package leaflet that accompanies this letter**
- **Additional copies of the correct package leaflet are available on https://www.medicines.org.uk/emc/product/1801/pil or from the company contact point**

Batch details:

Product Name and MA Number	Active ingredients	Product Code	Pack size	Batch Numbers
Tisseel Ready to use Solutions for sealant PL 00116/0627	Human fibrinogen, aprotinin, human thrombin, calcium chloride dihydrate	5500387	2ml	D8W169AE
		5500388	4ml	D8W164AA
		5500389	10ml	D8W166AA

Please ensure all relevant staff are made aware of the content of this letter and that the information is communicated to patients.

Baxter can confirm the content of the section of the package leaflet intended to provide information to patients is correct.

Baxter Healthcare Ltd
Caxton Way / Thetford / Norfolk / IP24 3SE / Great Britain
T 01842 767000 **F** 01842 767099
Registered Office: Caxton Way / Thetford / Norfolk / IP24 3SE Registered in England No. 461365

The following information is incomplete in the package leaflet technical information section intended for healthcare professionals in the batches listed above:

Approved Text	Incomplete text
Instructions for use and handling and disposal	
Do NOT apply the two components of TISSEEL separately. Both components must be applied together. Do NOT expose TISSEEL to temperatures above 37 °C. Do NOT microwave. Do NOT thaw the product by holding it in your hands.	Note: Do not thaw by holding product in your hands. Do not microwave.
Do NOT use TISSEEL 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. 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	Not Included
Handling and Preparation	
Using sterile technique, transfer the sterile inner pouch and contents onto the sterile field.	Not Included
Administration	
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 on any account. • 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. 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.	The protective syringe cap should not be removed until thawing is complete and application tip is ready to be attached. Do not use TISSEEL unless it is completely thawed and warmed (liquid consistency). Thawed products should be inspected visually for particulate matter and discoloration prior to administration.
Expel all air from the syringe prior to attaching any application device.	Not Included

Baxter Healthcare Ltd
Caxton Way / Thetford / Norfolk / IP24 3SE / Great Britain
T 01842 767000 **F** 01842 767099
Registered Office: Caxton Way / Thetford / Norfolk / IP24 3SE Registered in England No. 461365

Please ensure the approved Summary of Product Characteristics and package leaflet are followed. A copy of the approved package leaflet is provided with this letter.

The Summary of Product Characteristics and package leaflet can also be found on the Electronic Medicines Compendium at the following link: https://www.medicines.org.uk/emc/product/1801

Additional copies of the Summary of Product Characteristics and package leaflet also can be obtained from Baxter Medical Information, with contact details below.

Call for reporting

Healthcare professionals are asked to report suspected adverse reactions to the Yellow Card Scheme electronically. Report via the website https://yellowcard.mhra.gov.uk/, the free Yellow Card app available from the Apple App Store or Google Play Store, and some clinical IT systems (EMIS, SystmOne, Vision, MiDatabank) for healthcare professionals. Suspected side effects can also be reported by calling 0800 731 6789 for free.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Adverse Events relating to Baxter products can also be reported direct to Baxter Pharmacovigilance on 01635 206360, or by email to vigilanceuk@baxter.com.
Any drug product quality complaints (including suspected defective medicines) relating to Baxter products can be reported directly to the Baxter Country Quality Assurance Team on 01604 704603, or by email to UK_SHS_QA_Complaints@baxter.com.

Company contact point

If you have any questions about this letter or require more information about Tisseel, please contact Baxter Medical Information on 01635 206345 or email medinfo_uki@baxter.com.

Yours faithfully

Annie Holms
Business Unit Director, UKI Advanced Surgery

Baxter Healthcare Ltd
Caxton Way / Thetford / Norfolk / IP24 3SE / Great Britain
T 01842 767000 **F** 01842 767099
Registered Office: Caxton Way / Thetford / Norfolk / IP24 3SE Registered in England No. 461365

Baxter

0756374

PACKAGE LEAFLET: INFORMATION FOR THE USER

TISSEEL Ready to use

Solutions for Sealant

Human fibrinogen, human thrombin, synthetic aprotinin, calcium chloride dihydrate

Please read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. WHAT TISSEEL IS AND WHAT IT IS USED FOR

What TISSEEL is

The name of your medicine is TISSEEL Ready to use.

Throughout this leaflet TISSEEL Ready to use will be called TISSEEL.

TISSEEL is a two-component tissue sealant, and it contains two of the proteins that make blood clot. These proteins are called fibrinogen and thrombin. When these proteins mix during application, they form a clot where the surgeon applies them.

TISSEEL is prepared as two solutions (Sealer Protein Solution and Thrombin Solution), which mix when applied.

What TISSEEL is used for

TISSEEL is a fibrin or tissue sealant. During surgery, tissues may bleed and it may not be possible for the surgeon to control this bleeding using stitches, or by applying pressure. TISSEEL is applied to the surface of tissues, either to control bleeding, or to stop (or prevent) leaks of other types of fluid, by creating a watertight seal.

TISSEEL can be used even if your blood does not clot properly, e.g. when you are being treated with heparin against thrombosis. It is also used as a tissue glue to achieve adhesion/sealing or as suture support in surgery. In addition, TISSEEL is used to fix mesh during hernia repair surgery.

The clot produced by TISSEEL is very similar to a natural blood clot and this means that it will dissolve naturally and leave no residue. However, aprotinin is added to increase the longevity of the clot and to prevent its premature dissolution.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE TISSEEL

Do not use TISSEEL in the following situations:
- TISSEEL must not be used for massive or brisk bleeding.
- TISSEEL MUST NOT be injected into blood vessels (veins or arteries), or into tissues. As TISSEEL forms a clot where it is applied, injecting TISSEEL may cause serious reactions. TISSEEL should only be applied to the surface of tissues as a thin layer where it is needed. If you are going to have a coronary bypass surgery, special care needs to be taken to avoid injecting TISSEEL into blood vessels
- If you are allergic (hypersensitive) to any of the active substances or any of the other ingredients of this medicine.
  TISSEEL contains a synthetic protein, called aprotinin. Even when this protein is applied in small areas, there is a risk of a reaction known as anaphylaxis, or a severe allergic (hypersensitive) reaction.

Take special care with TISSEEL
- **Life-threatening/fatal air or gas embolism (air getting into the blood circulation which can be serious or life-threatening) has occurred very rarely with the use of spray devices employing pressure regulators to administer fibrin sealants. This 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.**
- **Spray devices and the accessory tip provide instructions for use with recommendations for pressure ranges and to the spraying distance from the tissue surface.**
- **TISSEEL should be administered strictly according to the instructions and only with devices recommended for this product.**
- **When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored for possible occurrence of gas embolism.**
- If you have ever received TISSEEL or aprotinin before, your body may have become sensitive to it. It is possible you may be allergic to this material, even if there was no reaction to the first application. If you think you have received either product in a previous operation, you have to inform your doctor about this.
- If the surgeon or operating team sees any sign of an allergic reaction during the application of TISSEEL, they will stop using TISSEEL immediately and will take the adequate measures.

Taking or using other medicines

There are no known interactions between TISSEEL and other medicinal products.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Oxidised cellulose containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials.

TISSEEL with food and drink

Please ask your doctor. The doctor will decide if you are allowed to eat and drink before the application of TISSEEL.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will decide if you can use TISSEEL during pregnancy or breast-feeding.

The effects of TISSEEL on fertility have not been established.

Driving and using machines

TISSEEL will not affect your ability to drive or operate other types of machines.

Important information about some of the ingredients of TISSEEL

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

Important information about the potential risk of infection from donor human plasma

When medicines are made from human blood or plasma, certain steps are taken to prevent infections being passed on to patients. Blood and plasma donors are carefully selected to make sure that those at risk of carrying infections are excluded.

In addition, each donation and plasma pool is tested for signs of viruses or infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

3. HOW TO USE TISSEEL

- TISSEEL is only applied during a surgical operation. The use of TISSEEL is restricted to experienced surgeons who have been trained in the use of TISSEEL.

The amount of TISSEEL that will be used depends on a number of factors, including but not limited to the type of surgery, the surface area of tissue to be treated during your operation and the way TISSEEL is applied. The surgeon will decide how much is appropriate, and will apply just enough to form a thin, even layer over the tissue. If this does not seem to be enough, a second layer can be applied. However, avoid a reapplication of TISSEEL to a pre-existing polymerized TISSEEL layer as TISSEEL will not adhere to a polymerized layer. Separate, sequential application of the two components of TISSEEL must be avoided.

- During your operation, the surgeon will apply TISSEEL onto the relevant tissue surface, using the special application device provided. This device ensures that equal amounts of both components are applied at the same time – which is important for the optimal effect of TISSEEL.
- For hernia repair surgery the surgeon will apply Tisseel using spray or drops to fix the mesh in place.
- 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).
- Pressurised air or gas must not be used for drying the site.
- TISSEEL must be sprayed only onto application sites that are visible.

When applying TISSEEL using a spray device be sure to use a pressure and a distance from the tissue within the range 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	10-15cm	1.5-2.0 bar (21.5-28.5 psi).
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		

Recommended pressure, distance and devices for spray application of TISSEEL					
Laparo-scopic/ minimally invasive procedures	n.a.	Duplospray MIS Applicator 20cm	Duplospray MIS Regulator 1.5 bar	2 – 5 cm	1.2-1.5 bar (18-22 psi)
		Duplospray MIS Applicator 30cm			
		Duplospray MIS Applicator 40cm			
		Spray Set 360 Endoscopic Applicator with Snaplock			
		Spray Set 360 Endoscopic Applicator with Tether			
		Replaceable tip			

When spraying TISSEEL, 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 section 2).

If you take more TISSEEL than you should

TISSEEL is only applied during a surgical operation. It is applied by the surgeon and the amount of TISSEEL is determined by the surgeon.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Use in children

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, TISSEEL can cause side effects, although not everybody gets them. If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Side effects have been evaluated on the basis of the following frequency categories:

Very common: Affects more than one in 10.

Common: Affects 1 to 10 users in 100.

Uncommon: Affects 1 to 10 users in 1,000.

Rare: Affects 1 to 10 users in 10,000.

Very rare: Affects fewer than 1 out of 10,000 patients treated.

Not known: The frequency cannot be estimated from the available data.

The following side effects have been observed in treatment with TISSEEL :

General areas	Side Effect	Frequency
Infections and parasitic diseases	Postoperative wound infection	Common
Blood and lymphatic system disorders	Increase of fibrin degradation products	Uncommon
Immune system disorders	Hypersensitivity reactions	Not known
	Allergic (anaphylactic) reactions	Not known
	Anaphylactic shock	Not known
	Sensation of tingling, pricking or numbness of the skin	Not known
	Tightness of the chest	Not known
	Breathing difficulties	Not known
	Itching	Not known
	Reddening of the skin	Not known
Nervous system disorders	Sensory disturbance	Common
Cardiac disorders	Increase or drop in pulse rate	Not known
Vascular disorders	Axillary venous thrombosis	Common
	Drop in blood pressure	Rare
	Bruising	Not known
	Gas bubbles in the vascular system*	Not known
	Blood clot in blood vessels	Not known
	Blockage of an artery in the brain	Not known
Respiratory, and thoracic disorders	Dyspnoea	Not known
Gastrointestinal disorders	Nausea	Uncommon
	Intestinal obstruction	Not known
Skin and subcutaneous tissue disorders	Skin Rash	Common
	Hives	Not known
	Impaired healing	Not known
Musculoskeletal and connective tissue disorders	Pain in extremities	Common

General disorders and administration site conditions	Pain caused by the procedure	Uncommon
	Pain	Common
	Increased body temperature	Common
	Reddening of the skin	Not known
	Swelling through the accumulation of fluid in the body tissue (oedema)	Not known
Injury, poisoning and procedural complications	Accumulation of lymph or other clear bodily fluids near the operation site (seroma)	Very common
	Rapid swelling of dermis, subcutaneous tissue, mucosa and submucosa (angioedema)	Not known

* the introduction of air or gas bubbles in the vascular system have occurred when fibrin sealants are applied with devices using pressurized air or gas; this is believed to be caused by inappropriate use of the spray device (e.g. at higher than recommended pressure and in close proximity to the tissue surface.)

In patients who are treated with fibrin sealant, hypersensitivity reactions or allergic reactions may occur. Although they are rare, they may be severe.

The first signs of an allergic reaction may include

- transient reddening of the skin ("flushing")
- itching
- hives
- nausea, vomiting
- headache
- drowsiness
- restlessness
- burning and stinging at the application site
- tingling
- chills
- tightness of the chest
- swelling of lips, tongue, throat (which may result in difficulty to breathe and/or swallow)
- breathing difficulties
- low blood pressure
- increase or drop in pulse rate
- loss of consciousness due to a drop in blood pressure

In isolated cases, these reactions may progress to severe allergic reactions (anaphylaxis). Such reactions may be seen especially if the preparation is applied repeatedly, or administered to patients who have previously shown hypersensitivity to aprotinin or any other component of the product.

Even if repeated treatment with TISSEEL was well tolerated, a subsequent administration of TISSEEL or an infusion of aprotinin may result in severe allergic (anaphylactic) reactions.

The attending surgical team is well aware of the risk of reactions of this type and will immediately interrupt the application of TISSEEL on the occurrence of the first signs of hypersensitivity. In the case of severe symptoms emergency measures may be required.

The injection of TISSEEL into soft tissues may lead to local tissue damage.

The injection of TISSEEL into blood vessels (veins or arteries) may lead to the formation of clots (thromboses).

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

As TISSEEL is derived from plasma from blood donations, the risk of an infection cannot be excluded completely. However, the manufacturers take numerous measures to reduce this risk (see section 2).

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

Reporting side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcardor search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE TISSEEL

- Keep out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the container after "EXP".
- Store at ≤–20°C (in a freezer). The cold storage chain must not be interrupted until use.
- Store in the original package in order to protect from light
- After thawing, the solution must not be refrozen or refrigerated!

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What TISSEEL contains

TISSEEL contains two components:

Component 1 = Sealer Protein Solution:

The active substances contained in 1ml of the Sealer Protein solution are:

Human Fibrinogen, 72 - 110 mg/ml; Aprotinin (synthetic), 3000 KIU/ml.

The excipients are Human Albumin, L-Histidine, Niacinamide, Polysorbate 80, Sodium Citrate Dihydrate and Water for Injections.

Component 2 = Thrombin Solution:

The active substances contained in 1 ml of the Thrombin Solution are:

Human Thrombin, 500 IU/ml; Calcium Chloride Dihydrate, 40 µmol/ml.

The excipients are Human Albumin, Sodium Chloride and Water for Injections.

What TISSEEL looks like and the contents of the pack

Both components of TISSEEL Sealer Protein Solution and Thrombin Solution are filled in single-use double-chamber syringes made of polypropylene. Both components are colourless or pale yellow.

Each pack of TISSEEL contains

- One pre-filled double-chamber syringe with Sealer Protein Solution (with aprotinin), deep-frozen, in one chamber; and Thrombin Solution (with calcium chloride dihydrate), deep frozen, in the other chamber.
- One set of sterile accessory devices (device with 2 joining pieces and 4 application cannulas).

TISSEEL is available in the following pack sizes:

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

TISSEEL is available in pack sizes of 2 ml, 4 ml and 10 ml

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Baxter Healthcare
Caxton Way, Thetford,
Norfolk, IP24 3SE,
UK

Manufacturer

Takeda Manufacturing Austria AG
Industriestraße 67
A-1221 Vienna
Austria

This leaflet was last revised in 01/2022

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling and disposal

General

Before administering TISSEEL, take care that parts of the body outside the intended application area are adequately covered, so that the medicine does not adhere to tissue at undesired sites.

For surgical procedures that require minimal volumes of fibrin sealant, do not use the first few drops of Tisseel Ready to use. In order to ensure complete blending of the sealer protein component and the thrombin component, express the first few drops of the product from the application cannula immediately before use and dispose of them.

To prevent TISSEEL from adhering to gloves and instruments, wet these with saline before contact.

Some solutions that contain alcohol, iodine or certain types of metals (these are normally found in disinfectants or antiseptics) may reduce the ability of TISSEEL to work normally. These substances should be removed, as far as possible, before TISSEEL is applied.

The guideline for sealing surfaces is: One package of TISSEEL 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 depends on the size of the surface to be sealed.

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

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

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

Do NOT use TISSEEL 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. 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.

It is strongly recommended that every time you receive a dose of TISSEEL, the name and batch number of the product are recorded. This maintains a record of the batches used.

Handling and Preparation

The pre-filled double-chamber syringe is packed and hermetically sealed in two sterilized 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.

Tisseel in 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 - PRIMA Syringe: 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 and the plunger into the sterile area.

Table 2 - PRIMA Syringe: 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 - PRIMA Syringe: 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 - PRIMA Syringe: 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) product in bags		Warming times prior to use to 33°C to a maximum of 37°C in the incubator after thawing at RT product in bags
2 ml	80 minutes	+	11 minutes
4 ml	90 minutes	+	13 minutes
10 ml	160 minutes	+	25 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.

Administration

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 on any account.

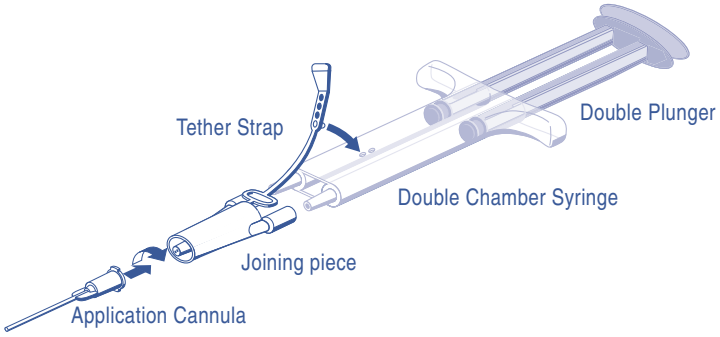
- Remove the syringe from the bags shortly before use.
- Use TISSEEL only when it is thawed and warmed completely (liquid consistency).
- Remove the protective cap from the syringe immediately before application.

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 application of TISSEEL use the pre-filled double-chamber syringe with the accessory devices provided with the product.

Operating Instructions

For application, connect the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution 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 the equal volumes are fed through the joining piece before being mixed in the application needle and ejected.



- Expel all air from the syringe prior to attaching any application device.
- Connect the double-chamber syringe nozzles to the joining piece and secure it 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 check that the connection is tight, 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 needle until you start actual application, as otherwise the aperture of the needle may clog.
- Apply the mixed Fibrin Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.
- When Tisseel 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 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.
- If application of the fibrin sealant components is interrupted, clogging occurs immediately in the needle. Only 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 mixing of the sealant components, the fibrin sealant starts to set within seconds, because 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, position 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.

Disposal

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

When applying TISSEEL using a spray device be sure to use a pressure and a distance from the tissue within the range 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	Recom-mended distance from target tissue	Recom-mended spray pressure
Open wound	Tisseel / Artiss Spray Set	n.a.	EasySpray	10-15cm	1.5-2.0 bar (21.5-28.5 psi).
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		
Laparo-scopic/ minimally invasive procedures	n.a.	Duplospray MIS Applicator 20cm	Duplospray MIS Regulator 1.5 bar	2 – 5 cm	1.2-1.5 bar (18-22 psi)
		Duplospray MIS Applicator 30cm			
		Duplospray MIS Applicator 40cm			
		Spray Set 360 Endoscopic Applicator with Snaplock			
		Spray Set 360 Endoscopic Applicator with Tether			
		Replaceable tip			

When spraying 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 section 2).