

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
2. What you need to know before you use TISSEEL
3. How to use TISSEEL
4. Possible side effects
5. How to store TISSEEL
6. Contents of the pack and other information

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 CO₂ 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 CO₂ 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		
Laparoscopic/ minimally invasive procedures	n.a.	Duplospray MIS Applicator 20cm	Duplospray MIS Regulator 1.5 bar	2-5 cm	1.2-1.5 bar (18-22 psi)
		Duplospray MIS Applicator 30cm			
		Duplospray MIS Applicator 40cm			
		Spray Set 360 Endoscopic Applicator with Snaplock			
		Spray Set 360 Endoscopic Applicator with Tether			
		Replaceable tip			

When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism (see 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
Nervous system disorders	Reddening of the skin	Not known
	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/yellowcard or 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 $\leq -18^{\circ}\text{C}$ (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 $\mu\text{mol/ml}$.

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 colorless 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 (Duo Set: 1 syringe plunger, 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

Baxter AG
Industriestraße 67
A-1221 Vienna
Austria

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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 cm².

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

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.

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. (Check that the temperature is within range by monitoring the water temperature with a thermometer and changing the water as necessary. When using a sterile water bath for thawing and warming, the pre-filled double-chamber syringe 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. Do not use TISSEEL unless it is completely thawed and warmed (liquid consistency).

Thaw pre-filled syringes in one of the three following options:

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 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 in 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.

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 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 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 shortly before use in order to allow for optimum blending of the two solutions. Respective thawing times in the incubator are also given in Table 3.

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

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

Note: Do not thaw by holding product in your hands.
Do not microwave.
After thawing do not refrigerate or refreeze.

To facilitate blending of the two solutions and allow for optimum solidification of the blend, the two sealant components must be warmed to 33-37°C. (The temperature of 37°C must, however, not be exceeded!)

The pre-filled double-chamber syringe should not be removed from the plastic bags until shortly before use and the protective caps of the syringes should not be taken off until shortly before application.

Administration

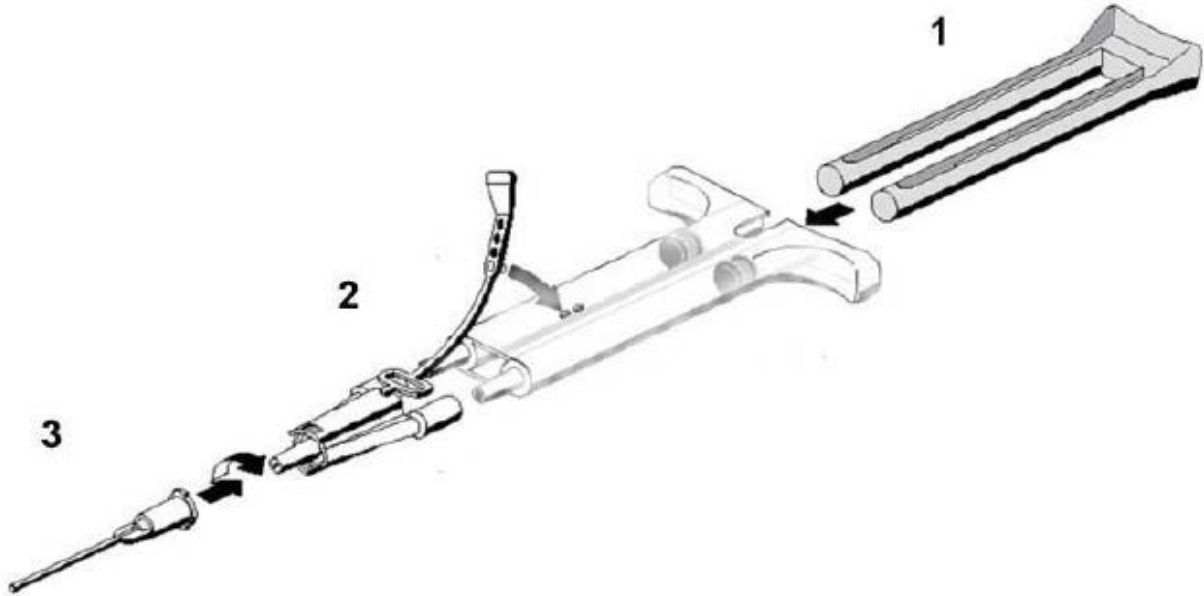
The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration.

Thawed, unopened pouches may be stored for up to 72 hours at controlled room temperature (not exceeding +25°C). Prior to administration, TISSEEL should be warmed to 33 – 37°C.

For application of TISSEEL use the pre-filled double-chamber syringe with the Duo Set 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.



- 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	Recommended distance from target tissue	Recommended spray pressure
Open wound	Tisseel / Artiss Spray Set	n.a.	EasySpray	10-15cm	1.5-2.0 bar (21.5-28.5 psi).
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		
Laparoscopic/ minimally invasive procedures	n.a.	Duplospray MIS Applicator 20cm	Duplospray MIS Regulator 1.5 bar	2-5 cm	1.2-1.5 bar (18-22 psi)
		Duplospray MIS Applicator 30cm			
		Duplospray MIS Applicator 40cm			
		Spray Set 360 Endoscopic Applicator with Snaplock			
		Spray Set 360 Endoscopic Applicator with Tether			
		Replaceable tip			

When spraying the TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism (see section 2).