

Baxter**NAME OF THE MEDICINAL PRODUCT**

TISSEEL Kit

Powders and Solvents for Sealant

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TISSEEL Kit contains 5 vials with the following active ingredients:

TISSEEL Powder for TISSEEL Solution,

Human, Steam Treated

After reconstitution of the powder, 1 ml of TISSEEL Solution contains:

Clottable protein	75 – 115 mg
thereof Fibrinogen	70 – 110 mg
Plasma fibronectin	2 – 9 mg
Factor XIII	10 – 50 U ¹
Plasminogen	40 – 120 µg

Aprotinin Solution, Solvent for TISSEEL Powder

Aprotinin, bovine 3000 KIU/ml²

Thrombin 4 Powder for Thrombin Solution

Human, Steam Treated

After reconstitution of the powder, 1 ml of Thrombin Solution contains:

Thrombin 4 IU³

Thrombin 500 Powder for Thrombin Solution

Human, Steam Treated

After reconstitution of the powder, 1 ml of Thrombin Solution contains:

Thrombin 500 IU³

Calcium Chloride Solution, Solvent for Thrombin Powder

Calcium Chloride 40 µmol/ml

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Powders and Solvents for Sealant.

CLINICAL PARTICULARS**Therapeutic Indications**

TISSEEL Kit is used to achieve hemostasis, to seal or glue tissue, and to support wound healing. In certain applications biocompatible material, such as collagen fleece, is used as a carrier substance or for reinforcement. Indications include, but are not limited to:

Hemostasis

Hemostasis in diffuse, intractable bleedings, after joint and bone surgery, adenoidectomy and tonsillectomy as well as after maxillo-dental surgery in patients with bleeding disorders, sealing of the prostatic bed after prostatectomy, etc.

Sealing

Coating and sealing of vascular prostheses, tympanoplasty, management of CSF fistulae and dura lesions, air-tight sealing of sutures and staples in lung parenchyma and pleura, of sutures in trachea, bronchus and esophagus, management of malignant pleural effusion, sealing of the lens after injuries with perforations, sealing of suture lines to prevent leakage of intestinal anastomoses, additional sealing of sutured microvascular anastomoses, etc.

Tissue Gluing

Gluing of parenchyma in surgery on the kidney, liver, spleen and pancreas, spongiosa grafting when packing bone cavities and defects, pleurodesis in spontaneous pneumothorax, fixation of skin grafts and flaps, fixation of osteochondral fragments and implants, gluing of peripheral nerves, plastic surgery after opening of the maxillary sinus, etc.

Support of Wound Healing

Skin grafting on devascularized and infected recipient sites, management of skin necroses and mucosal ulcers, incorporation of homologous bone grafts, etc.

Posology and Method of Administration**Posology**

The required dose of TISSEEL Kit depends on the size of the surface to be sealed or coated or on the size of the defect to be packed. It is also dependent on the application method chosen.

As a guideline for the gluing of surfaces one TISSEEL Kit 1.0 ml (i.e. 1 ml TISSEEL Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm².

When the fibrin sealant is applied by spray application the same quantity will be sufficient to coat an area of up to 100 cm², depending on the specific indication and the individual case.

To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the TISSEEL-Thrombin Solution, or the individual components, should be applied.

The setting rate of the fibrin sealant depends on the concentration of the Thrombin Solution used. While the fibrin sealant takes 30 to 60 seconds to set with a thrombin concentration of 4 IU/ml, this setting process will be complete within a few seconds if the higher thrombin concentration of 500 IU/ml is used. The higher thrombin concentration is required in order to achieve hemostasis whilst the lower thrombin concentration is suitable for sealing tissue because it allows time for approximation of the wound areas.

¹ One unit Factor XIII corresponds to the amount of Factor XIII contained in 1 ml fresh normal plasma.

² 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit).

³ One International Unit (IU) of Thrombin is defined as the activity contained in 0.0853 mg of the First International Standard of Human Thrombin.

Methods of Administration

After preparation of TISSEEL Kit as described in Instructions for Use, Handling and Disposal, the fibrin sealant components can be applied by the following methods:

I) Simultaneous Application

- using DUPLOJECT Two-Syringe Clip, Joining Piece, and Application Needle
- using DUPLOJECT Two-Syringe Clip, DUPLOJECT Spray Set, and TISSOMAT Pressure Control Device
- using DUPLOJECT Two-Syringe Clip and DUPLOCATH Application Catheters
- using DUPLOJECT Two-Syringe Clip and DUPLOTIP Applicators
- by premixing (e.g., with spongiosa or bone chips) using DUPLOJECT Two-Syringe Clip and Joining Piece

Note: For simultaneous application by premixing use of a Thrombin Solution of 4 IU Thrombin/ml is recommended.

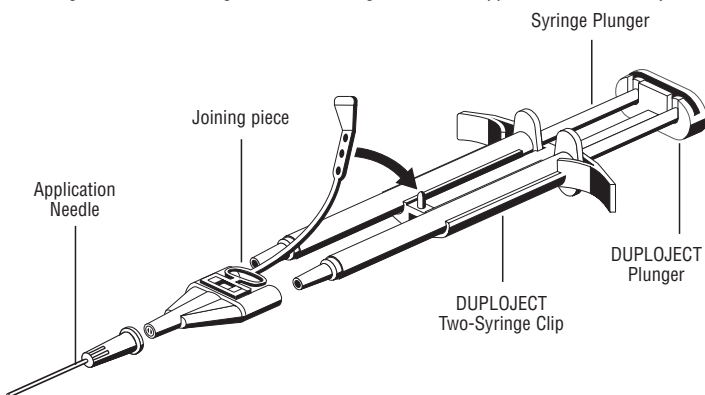
II) Sequential Application

I. Simultaneous Application

The DUPLOJECT Two-Syringe Clip allows for simultaneous application of equal quantities of TISSEEL Solution and Thrombin Solution and ensures that the two components are quickly and thoroughly mixed to give the TISSEEL-Thrombin Solution. This is essential for the fibrin sealant to gain optimum strength.

a) Simultaneous Application Using DUPLOJECT Two-Syringe Clip, Joining Piece and Application Needle:

The DUPLOJECT Two-Syringe Clip holds two identical disposable syringes and has a common plunger, which ensures that equal volumes of the two components are fed through a common Joining Piece before being mixed in the Application Needle and ejected.



Operating Instructions

- Place the two syringes filled with TISSEEL Solution and Thrombin Solution into the clip. Both syringes should be filled with equal volumes.
- Connect the nozzles of the two syringes to the Joining Piece ensuring that they are firmly fixed. Secure the Joining Piece by fastening the pull strap to the DUPLOJECT Two-Syringe Clip. Should the pull strap tear, use the spare Joining Piece. If none is available, further use is still possible but tightness of the connection needs to be ensured to prevent any risk of leaking.
- Fit an Application Needle onto the Joining Piece.

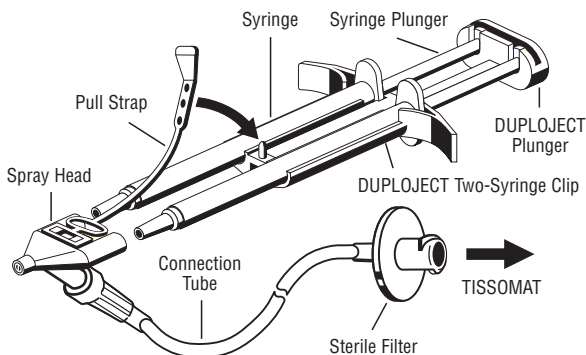
Do not expel the air remaining inside the Joining Piece or Application Needle unless you start actual application as the aperture of the needle may clog otherwise.

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

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

b) Simultaneous Application Using DUPLOJECT Two-Syringe Clip, DUPLOJECT Spray Set and TISSOMAT Pressure Control Device:

In the management of extensive wound areas – as in tissue grafting (skin) or for the arrest of oozing hemorrhages – TISSEEL Solution and Thrombin Solution can be applied with this device combination.



The Spray Head is attached to the two syringe tips. By pressing the common plunger, the two solutions are passed to two adjacent outlets, which are encircled by the pressure gas exit. The gas flow atomizes and mixes the two components, which can then be sprayed simultaneously using propellant gas (compressed air or nitrogen; pressure: approx. 1.5 – 2 bar, 5 – 20 l/min), sterilized by means of a sterile filter, and **the minimum spraying distance being 10 cm**. The volume of the solutions ejected is controlled by the DUPLOJECT Plunger. The pressure and flow rate of the propellant gas are controlled with the TISSOMAT Pressure Control Device. The DUPLOJECT Spray Set must be used only in connection with the TISSOMAT Pressure Control Device.

The user is cautioned against the spray application of TISSEEL Solution and Thrombin Solution with devices produced by other manufacturers.

Note: A detailed description of this application method is included in the instructions for use of the DUPLOJECT Spray Set and the TISSOMAT Pressure Control Device.

c) Simultaneous Application Using DUPLOJECT Two-Syringe Clip and DUPLOCATH Application Catheters:

In operation sites where access is difficult, in minimally invasive surgery through a trocar, or when using an endoscope, TISSEEL Solution and Thrombin Solution can be applied using this approach.

Note: A detailed description of this application method is included in the instructions for use of the DUPLOCATH Application Catheter.

d) Simultaneous Application Using DUPLOJECT Two-Syringe Clip and DUPLOTIP Applicators:

In operation sites where access is difficult, in microsurgical procedures (e.g., in Neurosurgery, ENT) and in minimally invasive surgery, TISSEEL Solution and Thrombin Solution can be applied using this approach.

Note: A detailed description of this application method is included in the instructions for use of the DUPLOTIP Applicator.

e) Simultaneous Application by Premixing:

This type of application is only recommended when using a thrombin concentration of 4 IU/ml. Mix equal volumes of the two fibrin sealant components and apply them to the recipient site. About one minute is available for mixing the components, applying the sealant and approximating the wound areas. The TISSEEL-Thrombin Solution can be premixed e.g., with spongiosa to pack bone defects.

II. Sequential Application

For this method of application the two syringes are removed from the DUPLOJECT Two-Syringe Clip and used separately.

Apply TISSEEL Solution to one of the surfaces to be sealed and an equal quantity of Thrombin Solution to the other; then join the two surfaces. If the high thrombin concentration is chosen, rapid solidification of the fibrin sealant leaves very little time for approximation and adaptation of the surfaces.

Note: After the two components have been applied, approximate the wound areas. Fix or hold the glued parts with continuous gentle pressure in the desired position for about 3 – 5 minutes to ensure that the setting fibrin sealant adheres firmly to the surrounding tissue.

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

Contraindications

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

Known hypersensitivity to aprotinin (or other bovine proteins) or known hypersensitivity to any other component of TISSEEL Kit.

Injection into the nasal mucosa must be avoided, as severe allergic-anaphylactoid reactions have been observed and thromboembolic complications may occur in the area of the ophthalmic artery.

Special Warnings and Special Precautions for Use

Special Warnings

TISSEEL Powder and Thrombin Powder are made from human plasma. When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is, however, reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV
- testing of plasma pools for genomic material of HIV-1, HIV-2, HAV, HBV, HCV and parvovirus B19.
- viral inactivation/removal procedures included in the production process that have been validated using target and/or model viruses. These procedures are considered effective for HIV-1, HIV-2, HAV, HBV and HCV.

The viral inactivation/removal procedures 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 red cell turnover (e.g., in hemolytic anemia).

Special Precautions

1. For patients with allergic diathesis or known hypersensitivity to medicinal products, and for patients previously having received aprotinin, careful risk/benefit assessment must be carried out. It is recommended to administer antihistamines prior to aprotinin treatment.
2. **TISSEEL Kit should not be applied intravascularly, since this may lead to anaphylactic reactions and/or thromboembolic complications, which both may be life-threatening. Especially in coronary bypass surgery, TISSEEL Kit should be applied with caution to minimize any risk of intravascular application.**
3. **Soft tissue injection of TISSEEL Kit carries the risk of an anaphylactoid reaction.** Therefore, TISSEEL and/or Thrombin Solution/s should only be applied topically. However, in well-justified cases where the injection of TISSEEL and/or Thrombin Solution/s into a tissue is indicated, careful risk/benefit analysis of the individual case must be carried out.

In the management of ulcer bleedings by way of submucous application of fibrin sealant in hollow organs (stomach, duodenum), the following has been observed:

- Insertion of the cannula into the organ wall has resulted in accidental perforation, which in rare cases may result in injuries of adjacent organs or vessels.
- In one case, the inadvertent injection of fibrin sealant into a vessel resulted in severe ischemic complications secondary to thromboembolic events in the adjacent intra-abdominal organs (liver, pancreas, stomach, spleen). In order to minimize the risk of such complications the following must be considered under all circumstances:

Application of more than 1 ml of fibrin sealant (0.5 ml TISSEEL Solution and 0.5 ml Thrombin Solution) at a single injection site must be avoided. If submucous injection of fibrin sealant has no hemostatic effect or only an insignificant effect, or if the bleeding recommences with the same intensity after some time with the application catheter still in place, the possibility of an inadvertent injection of fibrin sealant into a vessel has to be taken into consideration.

If hemostasis cannot be achieved by applying the above-mentioned single doses, adequate surgical procedures will have to be performed.

- Injection into the submucous membranes of the stomach or the duodenum may in rare cases lead to the formation of a local intramural hematoma, which may, in particular in the area of the duodenal wall, cause compression of the pancreatic duct. As a consequence, symptoms suggestive of acute pancreatitis may develop.
4. TISSEEL Kit should not be used for the sealing of neuroanastomoses, as the high aprotinin content of the TISSEEL Solution (3000 KIU/ml) delays absorption of the fibrin seal and it cannot be ruled out that this may cause fibrosis*.
 5. Caution must be used when applying fibrin sealant using pressurized gas. Any application of pressurized gas may be associated with a potential risk of gas emphysema, tissue rupture, gas entrapment with compression, or air embolism, which may be life-threatening. Consequently spraying of the fibrin sealant should not be carried out in enclosed body areas. The spraying of fibrin sealant, for which propellant gas (compressed air or nitrogen; pressure: approx. 1.5–2 bar, 5–20 l/min), sterilized by means of a sterile filter, is used, may be carried out only under visual control by using the TISSOMAT Pressure Control Device, **the minimum spraying distance being 10 cm.** The user is cautioned against the spray application of TISSEEL Solution and Thrombin Solution with devices provided by other manufacturers. The TISSOMAT Pressure Control Device and the DUPLJECT Spray Set are available from a BAXTER representative.
 6. As TISSEEL and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals (e.g., in disinfectants), any such substances should be removed before application.
 7. If possible, cover all tissue adjacent to the site of sealing before applying TISSEEL and Thrombin Solutions.
 8. To prevent fibrin sealant from adhering to gloves and instruments, wet these with saline before contact.
 9. It is strongly recommended that every time that TISSEEL Kit is administered to a patient, the name and the batch number of the product are recorded.

Interactions with Other Medicaments and Other Forms of Interaction

None known. TISSEEL Kit can even be applied in fully heparinized patients (e.g., extracorporeal circulation).

Pregnancy and Lactation

No undesirable effects during pregnancy or lactation have been reported.

According to generally recognized recommendations, medicinal products should be given during pregnancy or lactation only when strictly indicated.

Effects on Ability to Drive and Use Machines

Not relevant.

Undesirable Effects

The undesirable effects reported in the listing hereafter are based on post-market experience for this type of product. Their frequency has been evaluated by using the following criteria: very common ($\geq 10\%$), common ($< 10\% - \geq 1\%$), uncommon ($< 1\% - \geq 1\%$), rare ($< 1\% - \geq 1/10\,000$) and very rare ($< 1/10\,000$).

The undesirable effects listed below reflect the type of undesirable effects that have been or may be reported with TISSEEL Kit.

Their incidence rate is $< 1/10\,000$, i.e. very rare

Cardiac disorders

- Bradycardia, Tachycardia

Gastrointestinal disorders

- Nausea

General disorders and administration site disorders

- Hypersensitivity reactions

Immune system disorders

- Anaphylactic reactions, Allergic reactions, Anaphylactic shock, Urticaria

Injury, poisoning and procedural complications

- Anaphylactoid reactions

Investigations

- Drop in blood pressure

Respiratory, thoracic and mediastinal disorders

- Dyspnea

Skin and subcutaneous tissue disorders

- Pruritus

Vascular disorders

- Flush, (severe) Hypotension, Thromboembolic complication

Anaphylactic and anaphylactoid reactions may occur very rarely following the repeated administration of TISSEEL Kit, systemic administration of aprotinin, and/or known hypersensitivity against aprotinin, if no prophylactic pre-medication is given.

Even if a second treatment with TISSEEL Kit was well tolerated, a subsequent administration of TISSEEL Kit or systemic administration of aprotinin may result in severe anaphylactic reactions. Symptoms associated with allergic/anaphylactic reactions include flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension, and anaphylactic shock.

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

In very rare cases, these reactions may also occur in patients receiving aprotinin or TISSEEL Kit for the very first time.

TISSEEL Kit should not be applied intravascularly, since this may lead to anaphylactic reactions and/or thromboembolic complications, which both may be life-threatening. Especially in coronary bypass surgery, TISSEEL Kit should be applied with caution to minimize any risk of intravascular application.

Soft tissue injection of TISSEEL Kit carries the risk of an anaphylactoid reaction. Therefore, TISSEEL and/or Thrombin Solution/s should be applied topically only. How-

* For the sealing of neuroanastomoses, usually a TISSEEL Solution with about 100 KIU Aprotinin/ml is used so that the fibrin sealant is completely absorbed within a short time (about 2 days).

A suitable concentration can be obtained as described in Instructions for Use, Handling and Disposal: I. Preparation of TISSEEL Solution – "Note".

ever, in well-justified cases where the injection of TISSEEL and/or Thrombin Solution/s into a tissue is indicated, careful risk/benefit analysis of the individual case must be carried out (see also Special Precautions).

For information on viral safety, see Special Warnings.

Overdose

TISSEEL Kit should only be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

PHARMACOLOGICAL PROPERTIES

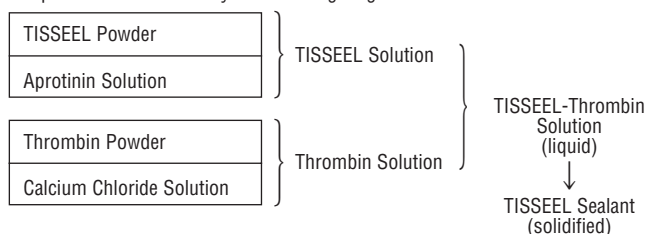
Pharmacodynamic Properties

Pharmacotherapeutic group: Blood and blood forming organs/antihemorrhagics/vitamin K and other hemostatics/blood coagulation factors.

ATC code: B02BC

TISSEEL Kit is a biological two-component sealant. The components (TISSEEL Solution and Thrombin Solution) are mixed during or immediately before application (see Methods of Administration). This results in a viscous TISSEEL-Thrombin Solution that quickly sets to form a white, elastic mass (fibrin sealant), which firmly adheres to tissue. This process simulates the key features of the physiological coagulation process and is used to achieve hemostasis, to seal or glue tissue, and to support wound healing.

The process is illustrated by the following diagram:



Pharmacokinetic Properties

When the fibrin sealant components come into contact, polymerization (fibrinogen to fibrin conversion and fibrin cross linking) starts immediately and results in the setting of the fibrin sealant within seconds.

The solidified fibrin sealant is completely absorbed in the course of wound healing.

PHARMACEUTICAL PARTICULARS

List of Excipients

Excipients of TISSEEL Powder

Human Albumin
Glycine
Sodium Chloride
Sodium Citrate
Tyloxapol (Triton WR1339)

Excipients of Aprotinin Solution

Water for Injections

Excipients of Thrombin Powder

Sodium Chloride
Glycine

Excipients of Calcium Chloride Solution

Water for Injections

Incompatibilities

This medicinal product must not be mixed with medicinal products other than those mentioned in Instructions for Use, Handling and Disposal.

TISSEEL and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals.

Shelf Life

Do not use after the expiry date stated on the outer label.

Reconstituted TISSEEL and Thrombin Solutions must be used within 4 hours.

Reconstituted product must not be returned to the refrigerator.

Special Precautions for Storage

Keep out of the reach and sight of children.

Store TISSEEL Kit at +2°C to +8°C, protected from light. Do not freeze.

The Kit for Reconstitution and Application (DUPLOJECT System) can be stored at +2°C to +8°C or, alternatively, at room temperature.

Nature and Contents of Container

Nature of containers:

All components of TISSEEL Kit are filled into glass containers (TISSEEL Powder, 5.0 ml filling size: type II glass; all other vials: type I glass) conforming to Ph. Eur. requirements. The vial containing TISSEEL Powder is equipped with a magnetic stirrer.

The containers are closed by halogenobutyl rubber stoppers.

Contents:

Each pack of TISSEEL Kit contains

- 1 vial containing TISSEEL Powder;
- 1 vial containing Thrombin Powder 4 IU/ml;
- 1 vial containing Thrombin Powder 500 IU/ml;
- 1 vial containing Aprotinin Solution;
- 1 vial containing Calcium Chloride Solution;
- 1 kit for reconstitution and application (DUPLOJECT System)

TISSEEL Kit is available in pack sizes of 1.0 ml, 2.0 ml, and 5.0 ml.

Not all pack sizes may be available on the market.

Kit for Reconstitution and Application (DUPLOJECT System)

Each Kit for Reconstitution and Application (DUPLOJECT System) contains one single-sterile set of devices for reconstitution under non-sterile conditions, and one double-sterile set of devices for application under sterile conditions.

The set for reconstitution includes 2 disposable needles plus one blue-scaled disposable syringe and one black-scaled disposable syringe.

The set for application includes 2 disposable needles, one blue-scaled disposable syringe and one black-scaled disposable syringe, one DUPLOJECT Two-Syringe Clip, 2 Joining Pieces and 4 Application Needles.

The Kit for Reconstitution and Application (DUPLOJECT System) is sterile and non-pyrogenic in the unopened and undamaged package and is sterilized by exposure to ethylene oxide.

The Kit for Reconstitution and Application (DUPLOJECT System) is for single use only. Do not re-sterilize!

Further accessories can be obtained from a BAXTER representative:

DUPLOJECT Spray Set Sterile disposable. To be used only together with the TISSOMAT Pressure Control Device.

TISSOMAT Pressure Control Device

DUPLOCATH Application Sterile disposable.

Catheters 25, 180 and 35 M.I.S.

DUPLOTIP Applicators Sterile disposable.

Instructions for Use, Handling and Disposal

Preparation of Components

Prior to reconstitution of the fibrin sealant components the rubber stoppers of all vials should be cleansed.

I. Preparation of TISSEEL Solution (First Component)

The TISSEEL Powder is dissolved with the Aprotinin Solution of 3000 KIU/ml to form TISSEEL Solution. To obtain a lower aprotinin concentration, dilute Aprotinin Solution with sterilised water for injections.

Note: For nerve sealing use an aprotinin concentration of approx. 100 KIU/ml. To obtain this concentration, dilute 0.2 ml with 5 ml of sterilised water for injections.

When packing bone defects with a mixture of fibrin sealant and spongiosa, aprotinin is not usually added. Dissolution of the TISSEEL Powder is therefore carried out using the required quantity of sterilised water for injections.

TISSEEL Powder is reconstituted using the FIBRINOTHERM warming and stirring device (recommended method). Alternatively, a sterile water bath at a temperature of 37°C can be used.

Reconstitution Using the FIBRINOTHERM Device:

The FIBRINOTHERM device maintains a constant temperature of 37°C. It also shortens the dissolution time of the TISSEEL Powder by rotating the magnetic stirrer contained in each TISSEEL Powder vial.

1. Place the vials containing TISSEEL Powder and Aprotinin Solution into the appropriate openings of the FIBRINOTHERM device and preheat the vials for 3 minutes.
2. Transfer the Aprotinin Solution into the vial containing the TISSEEL Powder using one needle and the blue-scaled syringe provided in the single-sterile kit for reconstitution. Place the TISSEEL Powder vial into the stirring well of the FIBRINOTHERM device (use the appropriate adaptor, if necessary) and stir until complete dissolution.

For further instructions please refer to the instructions for use of the FIBRINOTHERM device.

Reconstitution Using a Water-Bath:

1. Preheat the vials containing the TISSEEL Powder and the Aprotinin Solution for about 10 minutes in a water-bath at a temperature of 37°C. (Avoid heating beyond 40°C.)
2. Transfer the Aprotinin Solution into the vial containing the TISSEEL Powder using one needle and the blue-scaled syringe provided in the single-sterile kit for reconstitution.
3. Return the TISSEEL Powder vial to the water-bath at 37°C for one minute.
4. Swirl briefly but avoid excessive frothing. Then return the vial to the water-bath and check periodically for complete dissolution (see "Note").

Note: Keep the TISSEEL Solution at 37°C without stirring if it is not used immediately. To ensure homogeneity stir or swirl briefly before drawing up the TISSEEL Solution into the blue-scaled syringe provided in the double-sterile kit for application.

Always check that the TISSEEL Powder is fully dissolved: Reconstitution is complete as soon as no undissolved particles are visible when holding the vial against the light. If particles are present, keep the vial at 37°C for a few more minutes and agitate or stir the solution until complete dissolution.

Withdraw the reconstituted TISSEEL Solution from the vial under sterile conditions.

II. Preparation of Thrombin Solution (Second Component)

The Thrombin Powder is dissolved with the Calcium Chloride Solution of 40 µmol/ml to form Thrombin Solution. Depending on the thrombin concentration required, either transfer the contents of the Calcium Chloride Solution vial into the Thrombin 500 vial (quick solidification) or Thrombin 4 vial (slow solidification). Use the second needle and the black-scaled syringe provided in the single-sterile kit for reconstitution.

Swirl briefly to dissolve the lyophilized material and then keep the Thrombin Solution at 37°C until used. To warm the Thrombin Solution either the FIBRINOTHERM device or a water bath can be used. Prior to use draw up the Thrombin Solution from the vial using the second needle and the black-scaled syringe provided in the double-sterile kit for application.

Note: Syringes and needles used for the reconstitution of one component must not be re-used for the dilution of Aprotinin Solution or the reconstitution of the other component, as this would lead to solidification of that component in the vial or syringe.

Disposal of Product and Devices

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

MANUFACTURER

Baxter AG, Vienna, Austria

DATE OF REVISION OF THE TEXT

11/2003

TISSEEL, DUPLOCATH, DUPLOJECT, FIBRINOTHERM and TISSOMAT are trademarks of Baxter AG. BAXTER is a trademark of Baxter International Inc. DUPLOTIP is a trademark of Baxter International Inc. and Baxter Healthcare SA.

6208110EV07

TISSEEL™ DUO-500**Two-Component Fibrin Sealant
deep-frozen****Presentation**

Two deep-frozen solutions in two preloaded syringes

Manufactured by

Baxter AG, Vienna, Austria

COMPOSITION

TISSEEL DUO-500 is a biological two-component sealant of human origin, consisting of

TISSEEL Solution (with aprotinin) deep-frozen and
Thrombin Solution 500 (with calcium chloride) deep-frozen.

The active constituents of these two components are as follows:

TISSEEL Solution deep-frozen

1 ml contains:

Total protein	100 – 130 mg
Clottable protein	75 – 115 mg
thereof Fibrinogen	70 – 110 mg
Plasma fibronectin	2 – 9 mg
Factor XIII	10 – 50 U ¹
Plasminogen	40 – 120 µg
Aprotinin (bovine)	3,000 KIU ²

Thrombin Solution 500 deep-frozen

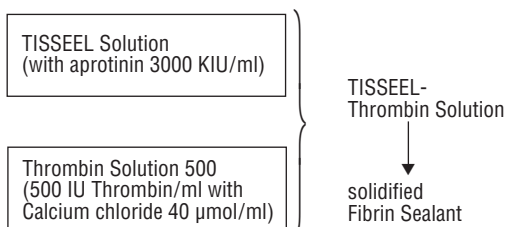
1 ml contains:

Thrombin	500 IU ³
Calcium chloride	40 µmol

PROPERTIES AND EFFECT

TISSEEL DUO-500 is a biological two component sealant. The components (TISSEEL Solution and Thrombin Solution) come deep-frozen, in preloaded syringes, and have to be defrosted prior to use. They are mixed during or immediately before application (see Methods of Application). This results in a viscous TISSEEL-Thrombin Solution that quickly sets to form a white, elastic mass, which firmly adheres to tissue. This process simulates the key features of the physiological coagulation process and is used to achieve hemostasis, to seal or glue tissue and to support wound healing. In the course of wound healing the solidified Fibrin Sealant is completely absorbed.

The process is illustrated by the following diagram:

**INDICATIONS**

TISSEEL DUO-500 is used to achieve hemostasis, to seal or to glue tissue, and to support wound healing. In certain applications biocompatible material, such as collagen fleece, is used as a carrier substance or for reinforcement.

TISSEEL DUO-500 can even be applied in fully heparinized patients (e.g. extracorporeal circulation).

Indications include, but are not limited to:

Hemostasis

Hemostasis in diffuse, intractable bleedings, after joint and bone surgery, adenoidectomy and tonsillectomy, as well as after maxillofacial surgery in patients with bleeding disorders, sealing of the prostatic bed after prostatectomy, etc.

Sealing

Coating and sealing of vascular prostheses, tympanoplasty, management of C.S.F. fistulae and dura lesions, treatment of premature rupture of the membranes in pregnancy by sealing of the lower amniotic region, air-tight sealing of sutures in lung parenchyma and pleura, of sutures in trachea, bronchus and oesophagus, management of malignant pleural effusion, sealing of the lens after injuries with perforations, sealing of suture lines to prevent leakage of intestinal anastomoses, additional sealing of sutured microvascular anastomoses, etc.

Tissue gluing

Gluing of parenchyma in surgery on the kidney, liver, spleen, and pancreas, pleurodesis of spontaneous pneumothorax, fixation of skin grafts and flaps, fixation of osteochondral fragments and implants, plastic surgery after opening the maxillary sinus, etc.

¹ One unit Factor XIII corresponds to the amount of Factor XIII contained in 1 ml of fresh normal plasma.

² 3,000 Kallidinogenase Inactivator Units (KIU) equal 3.4 European Pharmacopoeia Units (EPU).

³ One International Unit (IU) of Thrombin is defined as the activity contained in 0.0853 mg of the First International Standard of Human Thrombin (Code 70/157).

Support of wound healing

Skin grafting on devascularized and infected recipient sites, management of skin necroses and mucosal ulcers, incorporation of homologous bone grafts, etc.

CONTRAINDICATIONS

Known hypersensitivity to bovine proteins.

TISSEEL DUO-500 should not be used for the sealing of neuroanastomoses, as the high aprotinin content of the TISSEEL Solution (3,000 KIU/ml) delays absorption of the fibrin seal and it cannot be ruled out that this may cause fibrosis.¹

Injection into the nasal mucosa must be avoided, as severe allergic-anaphylactoid reactions have been seen and thromboembolic events may occur.

PRECAUTIONS FOR USE

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

If possible, cover all tissue adjacent to the site of sealing before applying TISSEEL and Thrombin Solutions.

INTERACTIONS

As TISSEEL and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals (contained e.g. in disinfectants), remove any such substances before applying the sealant.

PREGNANCY AND LACTATION

No adverse effects during pregnancy and lactation have been reported.

WARNINGS

Usually, TISSEEL and/or Thrombin Solution/s should not be injected. There is the risk of a possible anaphylactic reaction, and in intravascular administration also the risk of a thromboembolic event, both of which may be life-threatening. However, if in well-founded cases the injection of TISSEEL and/or Thrombin Solution/s into a tissue or vessel is indicated, careful risk/benefit analysis of the individual case is to be carried out.

In the submucous injection of fibrin sealant into hollow organs (stomach, duodenum), the following points are to be considered:

1. Insertion of the needle into the organ wall may result in accidental perforation, which in rare cases may injure adjoining organs or vessels.
2. No case of thromboembolic events following accidental vessel puncture and intravascular injection of fibrin sealant has so far been observed in the treatment of ventricular or duodenal ulcers, but cannot be excluded with certainty.
3. Injection into the submucous membrane may cause a mechanical dissection between the tunica mucosa and the tunica muscularis propria, which in rare cases may lead to vessel injury or the formation of an intramural hematoma.

Injection into the nasal mucosa must be avoided, as severe allergic-anaphylactoid reactions have been seen and thromboembolic events may occur.

Fibrin Sealant is sprayed using pressurized gas or compressed air. Any application of pressurized gas/compressed air may be associated with a risk of air embolism, gas emphysema, or tissue or organ rupture, which may be life-threatening.

Fibrin Sealant may be sprayed only by means of the TISSOMAT to application sites that are visible, the minimum required spraying distance being 10 cm. Thus, the DUPLOJECT system with the spray head must not be used in enclosed body areas. The user is cautioned against the spray application of TISSEEL with devices produced by other manufacturers. The TISSOMAT control device and the SPRAY SET may be obtained from Baxter.

When medicinal products prepared from human blood are administered, infectious diseases due to the transmission of infective agents – also of hitherto unknown origin – cannot be totally excluded. Therefore donors are selected according to strict criteria, plasma donations are tested and selected and plasma pools are controlled (Hyland Immuno Plasma Safety Program). The manufacturing process of TISSEEL Sealer Protein Concentrate and HUMAN THROMBIN includes measures for removal and inactivation of viruses (steam treatment).

Only plasma of healthy donors which has been tested with negative results for antibodies to HIV-1 and 2 and hepatitis C virus (HCV) as well as hepatitis B virus surface antigen (HB_sAg) is used for the manufacture of TISSEEL Sealer Protein Concentrate and HUMAN THROMBIN. The liver enzyme value (ALT) must not exceed the accepted threshold value. A sample of the plasma pool is also tested for HIV and HCV antibodies as well as for HB_sAg. In addition a test for virus genome sequences of HIV, HBV and HCV with the polymerase chain reaction (HIQ-PCR²) is carried out.

The polymerase chain reaction (PCR) is a highly sensitive method with which, in contrast to antibody testing, direct identification of virus genomes is possible. Only plasma pools in which no genomes of these viruses are detectable are released for further processing.

In addition, the Hyland Immuno Plasma Safety Program provides for Non-Returning Donor-Applicant Exclusion, Inventory Hold for each plasma donation and the Look-back Program.

The efficiency of these manufacturing steps employed during the production of TISSEEL Sealer Protein Concentrate and HUMAN THROMBIN, has been demonstrated in validation studies using human immunodeficiency virus (HIV), hepatitis A virus, and model viruses for hepatitis B and hepatitis C viruses (HBV, HCV), as well as for non-enveloped viruses.

In prospective international safety studies with coagulation factor concentrates virus inactivated by steam treatment, none of the patients, who were all previously untreated, showed any evidence of a transmission of hepatitis viruses or HIV, although the products were not HIQ-PCR tested at that time.

Pharmaco-epidemiological surveillance of TISSEEL DUO-500 has shown no product-

¹ For the sealing of neuroanastomoses, usually a TISSEEL Solution with about 100 KIU Aprotinin/ml (dilute Aprotinin Solution with aqua ad iniectionem) is used.

² HIQ-PCR is a quality-assured PCR testing program for genome equivalents of HIV, HBV and HCV. HIQ-PCR stands for Hyland Immuno Quality-Assured Polymerase Chain Reaction.

related transmission of the above mentioned agents.

DOSAGE

Required Volumes of TISSEEL Solution and Thrombin Solution

The required dose of TISSEEL Solution depends on the size of the surface to be sealed or coated or on the size of the defect to be packed. It is also dependent on the application method chosen.

As a guideline for the gluing of surfaces, 1 pack of TISSEEL DUO-500 1.0 ml (i.e. 1 ml of TISSEEL Solution **plus** 1 ml of Thrombin Solution) will be sufficient for an area of at least 10 cm². When the sealant is applied by spray application (DUPLOJECT System with Spray Set; see Methods of Application I.b) the same quantity will be sufficient to coat an area of 25 cm² to 100 cm², depending on the specific indication and the individual case.

As far as possible, the TISSEEL-Thrombin Solution should be applied in thin layers only to avoid unduly slow absorption of the fibrin seal.

PREPARATION

Defrosting and warming up of TISSEEL DUO-500

The syringe clip of the DUPLOJECT Application System holds the two preloaded syringes, all together sealed up in 2 plastic bags. The different appearance of both components is caused by their different protein concentrations. The inner bag is sterile both in- and outside. At room temperature thawing of both sealant components takes 20 minutes (0.5 ml size) to 90 minutes (5.0 ml size). For thawing and warming within several minutes, discard the two plastic bags and place TISSEEL DUO-500 in a sterile water bath (not beyond 37°C!)

Principally, warming up to – but not exceeding – 37°C is recommended, since it conduces the blending of the 2 solutions as well as solidification of the TISSEEL-Thrombin solution.

Do not take off protective caps of the syringes until shortly before application.

TISSEEL DUO-500 should only be used when, after thawing, the TISSEEL Solution has a viscous consistency similar to honey. (Air bubbles in the syringe holding the TISSEEL Solution slowly rise to the top when the DUPLOJECT System is tilted or turned upside down.)

If the TISSEEL Solution has the consistency of a gel, it must be assumed to have become denatured due to an interruption of the cold storage chain. In this case, the Fibrin Sealant must not be used.

The sealant components must be used within 36 hours after thawing.

Do not store in refrigerator after thawing!

METHODS OF APPLICATION

The sealant components can be applied by the following methods:

I) Simultaneous Application

- a) using DUPLOJECT plus Application Needle
- b) using DUPLOJECT plus Spray Set
- c) using DUPLOJECT plus Application Catheter

II) Sequential Application

Note:

After the 2 components have been applied, approximate the wound areas. Fix or hold the glued parts with continuous gentle pressure in the desired position for about 3–5 minutes to ensure that the setting sealant adheres firmly to the surrounding tissue.

After blending of the sealant components, the Fibrin Sealant starts to set within seconds on account of the high Thrombin concentration (500 IU/ml). When more time is required for application and approximation, e.g. for simultaneous application by premixing, a different presentation of TISSEEL should be chosen, where a Thrombin Solution of 4 IU/ml can be used.*

The DUPLOJECT System allows simultaneous application of equal quantities of TISSEEL Solution and Thrombin Solution and ensures that the 2 components are quickly and thoroughly mixed. This is essential for the seal to gain optimum strength.

Ia) Simultaneous Application Using DUPLOJECT and Application Needle

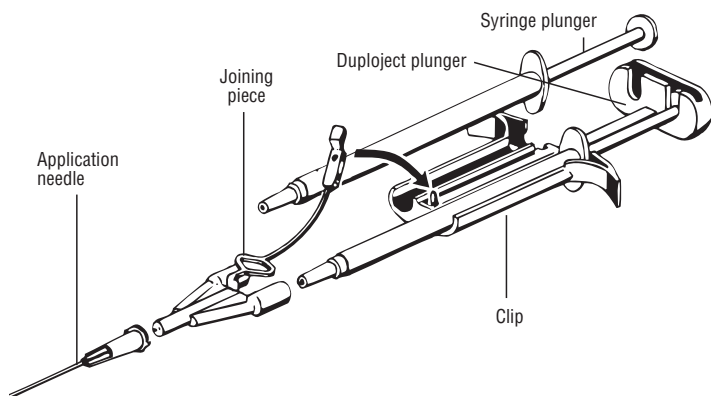
The DUPLOJECT System consists of a clip for two identical disposable syringes and a common plunger which ensures that equal volumes of the two components are fed through a common joining piece before being mixed in the application needle and ejected. The two preloaded syringes of TISSEEL DUO-500 are already inserted in the DUPLOJECT Clip.

Operating Instructions

- Remove the protective caps and connect the nozzles of both syringes to the joining piece ensuring that it is firmly fixed. Secure the joining piece by fastening the strap to the clip.
- Fit the application needle onto the joining piece.
Do not expel any air remaining inside the joining piece or application needle as the aperture of the needle may clog before application of the sealant.
- Apply the TISSEEL-Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

If application of the sealant components with DUPLOJECT and application needle is interrupted then replace the needle by a new one when sealing is resumed (3 spare needles are included).

Only replace the application needle immediately before sealing is resumed, otherwise the apertures of the joining piece will clog. (In this case use the spare joining piece provided).



Ib) Simultaneous Application Using DUPLOJECT, Spray Head and TISSEEL™

In the management of extensive wound areas – as in tissue grafting (skin) or for the stasis of oozing hemorrhages – TISSEEL can be applied with DUPLOJECT and Spray Head. The user is cautioned against the spray application of TISSEEL with devices produced by other manufacturers.

A detailed description of this application method is included in the leaflet of the Spray Set.

Ic) Simultaneous Application Using DUPLOJECT plus Application Catheter

In operation sites where access is difficult, or when using an endoscope or trocar, TISSEEL can be applied with DUPLOJECT and Application Catheter.

A detailed description of this application method is included in the leaflet of the Application Catheter.

II. Sequential Application

For this method of application the 2 syringes have to be removed from the syringe clip and are used separately.

Apply TISSEEL Solution to one of the surfaces to be sealed and an equal quantity of Thrombin Solution to the other; then join the 2 surfaces. As the high Thrombin concentration leads to rapid solidification of Fibrin Sealant, very little time is left for approximation of the surfaces.

SIDE EFFECTS

In cases of hypersensitivity to bovine proteins or after repeated administration allergic or anaphylactic reactions can occur on very rare occasions.

Should the symptoms require treatment, it should follow the guidelines of modern shock therapy, e.g. administration of antihistamines, corticoids, and/or adrenalin.

STORAGE

To be stored at -18°C or colder. The cold storage chain must not be interrupted until use.

Preparation must always be protected from light.

Do not store in refrigerator after thawing!

Store out of reach of children!

SHELF LIFE

TISSEEL DUO-500 must not be used after the expiry date indicated on the container and package labels.

After thawing the preparation must be used within 36 hours.

Do not store in refrigerator after thawing!

PACKS

TISSEEL™ DUO-500 2 x 0.5 ml

including: TISSEEL Solution (with Aprotinin) deep-frozen 0.5 ml
Thrombin Solution deep-frozen 0.5 ml

TISSEEL™ DUO-500 2 x 1.0 ml

including: TISSEEL Solution (with Aprotinin) deep-frozen 1.0 ml
Thrombin Solution deep-frozen 1.0 ml

TISSEEL™ DUO-500 2 x 2.0 ml

including: TISSEEL Solution (with Aprotinin) deep-frozen 2.0 ml
Thrombin Solution deep-frozen 2.0 ml

TISSEEL™ DUO-500 2 x 5.0 ml

including: TISSEEL Solution (with Aprotinin) deep-frozen 5.0 ml
Thrombin Solution deep-frozen 5.0 ml

Each pack includes 2 Joining Pieces for the syringes inserted in the DUPLOJECT® System and 4 Application Needles.

Accessories for use with the DUPLOJECT® System:

TISSEMAT™ Propellant gas control unit including foot switch, manometer, reducing valve, and pressure tube.

SPRAY SET Sterile disposable set consisting of connection tube with sterile filter, and 2 Spray Heads.

APPLICATION CATHETERS
Sterile disposable.