

PRODUCT MONOGRAPH

Pr ARTISS

Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated
4 IU (Slow Set)

Frozen Solutions for Thawing for Topical Application

Hemostatic and Tissue Adhesive Agent

Baxter Corporation
Mississauga, ON
Canada L5N 0C2

Date of Approval:
May 18, 2017

Submission Control No: 205080

Table of Contents

1. PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
DESCRIPTION	3
INDICATIONS AND CLINICAL USE.....	4
CONTRAINDICATIONS	5
WARNINGS AND PRECAUTIONS.....	6
ADVERSE REACTIONS.....	9
DRUG INTERACTIONS	11
DOSAGE AND ADMINISTRATION.....	11
OVERDOSAGE	18
ACTION AND CLINICAL PHARMACOLOGY	18
STORAGE AND STABILITY.....	19
DOSAGE FORMS, COMPOSITION AND PACKAGING	19
ACCESSORIES	20
2. PART II: SCIENTIFIC INFORMATION	21
PHARMACEUTICAL INFORMATION.....	21
CLINICAL TRIALS.....	22
DETAILED PHARMACOLOGY	25
TOXICOLOGY	27
3. PART III: CONSUMER INFORMATION.....	30
PATIENT COUNSELING INFORMATION	30

ARTISS

Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated, 4 IU/mL

1. PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	4 IU (Slow Set) - ARTISS Frozen Solutions for Thawing: 2.0 mL, 4.0 mL, 10.0 mL (total volume)	<i>For a complete listing see Dosage Forms, Composition and Packaging Section.</i>

DESCRIPTION

ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) is a two-component fibrin sealant made from pooled human plasma. When combined, the two components, Sealer Protein (Human) and Thrombin (Human), mimic the final stage of the blood coagulation cascade. ARTISS is intended only for topical administration.

Sealer Protein (Human)

Sealer Protein (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Sealer Protein (Human) is provided as a finished frozen liquid Sealer Protein-Aprotinin Solution pre-filled into one side of a double-chamber syringe (chamber containing Sealer Protein -Aprotinin Solution is marked as "1").

The active ingredient in Sealer Protein (Human) component is fibrinogen. In addition Factor XIII is co-purified with clottable protein from human plasma. No Factor XIII is added to the Sealer Protein (Human) manufacturing process, resulting in a Factor XIII level of 0.6-10 U/mL in the drug product. A Fibrinolysis Inhibitor, Aprotinin (Synthetic) is included in the Sealer Protein (Human) component to preclude premature fibrinolysis. To obtain Sealer Protein Concentrate (Human), cryoprecipitate derived from the plasma is dissolved in buffer solution, solvent/detergent treated, purified by precipitation and washing steps, vapor heat treated, formulated, sterile filtered, concentrated under vacuum and frozen in pre-filled syringes.

Thrombin (Human)

Thrombin (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Thrombin (Human) is provided as a finished frozen liquid Thrombin-Calcium Chloride Solution pre-filled into one side of a double-chamber syringe (chamber containing Thrombin-Calcium Chloride solution is marked as “2”).

The active ingredient human Thrombin is prepared from plasma through a series of separation and filtration steps followed by incubation of the solution with calcium chloride to activate prothrombin to thrombin. The solution subsequently undergoes ultra/diafiltration, vapor heat treatment, solvent/detergent treatment, purification by ion exchange chromatography, formulation, sterile filtration, filling and freezing in pre-filled syringes.

The setting rate of the Fibrin Sealant depends on the concentration of the human Thrombin as contained in the Thrombin-Calcium Chloride Solution used. The ARTISS thrombin component is provided in a 4 IU/mL concentration (ARTISS 4 IU, Slow Set). Time to clot formation/polymerisation may take up to one minute to set with a Thrombin concentration of 4 IU/mL. Use of ARTISS 4 IU (Slow Set) is appropriate for surgical procedures where sufficient time for manipulation of tissues and approximation of the wound areas is demanded to glue tissues (e.g. skin grafts, tissue flaps, etc.).

Sealer Protein (Human) and Thrombin (Human) are made from pooled human plasma. The vapor heat and solvent/detergent treatment steps used in the manufacturing process have been shown to be capable of significant viral reduction. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded (see *WARNINGS AND PRECAUTIONS* and *PHARMACEUTICAL INFORMATION*, and see *DOSAGE FORMS, COMPOSITION AND PACKAGING* for available package sizes and presentations).

INDICATIONS AND CLINICAL USE

ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent Detergent Treated) is indicated for:

- the fixation (gluing) of autologous skin grafts and tissue flaps.
- as an adjunct to hemostasis on subcutaneous tissue surfaces to treat burns in adult and pediatric patients.
- as an adjunct to adhere tissue flaps during facial rhytidectomy surgery (face-lift).

Geriatrics (> 65 years of age):

Efficacy and safety in use of ARTISS Fibrin Sealant has been evaluated in a clinical trial involving a small number of geriatric patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Pediatrics (1.1 – 16 years of age) or (< 16 years of age):

Efficacy and safety in the use of ARTISS Fibrin Sealant has been evaluated in a clinical trial involving a group of pediatric patients and was not found to be different from an adult population.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the *DOSAGE FORMS, COMPOSITION AND PACKAGING* Section of the product monograph.
 - ARTISS should not be used in individuals with a known hypersensitivity to Aprotinin.
- ARTISS is contraindicated for intravascular application. Intravascular application may result in life threatening thromboembolic events.
- For the treatment of massive brisk arterial or venous bleeding, ARTISS alone is not effective and is not indicated in this treatment.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Intravascular application of ARTISS can lead to intravascular coagulation, may result in life-threatening thromboembolic events and might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

ARTISS is not indicated for hemostasis in situations where a fast clotting of a sealant is required.

As with any other protein products, hypersensitivity or allergic/anaphylactic/anaphylactoid reactions may occur with the use of ARTISS, a fibrin sealant that contains aprotinin. In isolated cases, these reactions have progressed to severe anaphylaxis. Aprotinin, a monomeric polypeptide, is known to be associated with anaphylactic reactions. These reactions may also occur in patients receiving Aprotinin or ARTISS for the first time or even if first application was well tolerated, but generally risk may be increased if the preparation is applied repeatedly over time or in the same setting. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock. As with other aprotinin-containing products, the use of ARTISS should be documented in the patient's records, pointing out that ARTISS contains aprotinin.

In the event of anaphylactic/anaphylactoid or allergic-type hypersensitivity reactions, administration of ARTISS is to be discontinued. If possible, remove any applied, polymerized product from the surgical site. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction.

Caution must be used when applying fibrin sealant using pressurized air or gas (See DOSAGE AND ADMINISTRATION). Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and 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 when ARTISS is used during open wound surgery.

Solutions containing alcohol, iodine or heavy metals will interfere with the product's performance due to denaturation of proteins or other mechanisms.

General

Fibrin Sealant is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. This also applies to unknown or emerging viruses and other pathogens. The risk that such products will transmit an infectious agent has been reduced by screening plasma and by inactivating and removing certain viruses. Despite these measures, there may still carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The measures taken are considered effective for inactivation/removal of enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection) and individuals with immunodeficiency or increased red blood cell turnover.

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

This product must not be used in animals.

The user is cautioned against the spray application of ARTISS with devices produced by other manufacturers. The EASYSPRAY control device and the Spray Set may be obtained from Baxter. Only use application devices licensed for the administration of ARTISS.

ARTISS must not be used with the EASYSPRAY/ Spray Set system in enclosed body areas

When spraying ARTISS, 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

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

Only a thin layer of ARTISS should be applied to avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant. Excessive thickness of the fibrin layer may negatively interfere with the product's efficacy and the wound healing process (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Immediately before application, expel and discard the first several drops from the application cannula to ensure use of adequately mixed product. Separate, sequential application of the two components must be avoided.

If application is interrupted, clogging will occur quickly in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the aperture of the

joining piece facing the cannula is clogged, use the spare joining piece provided in the package.

Application Precautions

Only a thin layer of ARTISS should be applied. Excessive thickness of the fibrin sealant layer may interfere with the product's efficacy and the wound healing process.

It is strongly recommended that every time that ARTISS is applied to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

To reduce the risk of a potentially life-threatening gas embolism when applying ARTISS using the EASYSPRAY device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. Do not spray at a pressure above 2 bar or at a distance closer than 10 cm from the surface of the tissue. When spraying ARTISS, 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.

ARTISS spray application should only be used if it is possible to accurately judge the spray distance.

Solutions containing alcohol, iodine or heavy metals will interfere with the product's performance due to denaturation of proteins or other mechanisms. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of ARTISS.

Sexual Function/Reproduction

Animal reproduction studies have not been conducted with ARTISS. It is also not known whether it can affect reproduction capacity.

Special Populations

Pregnant Women: No experience.

Animal reproduction studies have not been conducted with ARTISS. It is also not known whether it can cause fetal harm when administered to a pregnant woman. Healthcare providers should balance the potential risks and only prescribe ARTISS if clearly needed.

See *WARNINGS AND PRECAUTIONS* for information on Parvovirus B19 infection.

Nursing Women:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARTISS is administered to a lactating woman.

Healthcare providers should balance the potential risks and only prescribe ARTISS if clearly needed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Allergic and/or anaphylactic reactions may occur in patients with a history of hypersensitivity against Aprotinin. Such reactions may be seen in the event of repeated administration, even if the first application was well tolerated. However, allergic and/or anaphylactic reactions may also occur in patients receiving ARTISS for the first time.

If symptoms require treatment to be initiated, this should be effected in the usual manner, as for instance with antihistamines, corticoids or adrenalin. No adverse events of this type were reported during the clinical trials for ARTISS.

Clinical Trial Adverse Drug Reactions (ADRs)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice.

The following ADRs have been reported from a clinical trial where ARTISS 4 IU (Slow Set) was used to affix split thickness sheet skin grafts to excised burn wounds (*see Part II Clinical Trials, trial number 550201*). Number of subjects was 138, all of them receiving both treatments: ARTISS 4 IU and control (staples). None of the events were classified as serious.

A total of 8 non-serious adverse events (AEs) were deemed related to the use of ARTISS 4 IU (Slow Set) by the investigator. Of the 8 related non-serious AEs, 5 were incidences of skin graft failure: 4 were graft detachment/non-adherence and 1 was graft necrosis. The graft detachment in 2 patients may have been related to the maximum thawing temperature (40°C) being exceeded during study product preparation. The 3 other non-serious AEs considered related to ARTISS 4 IU (Slow Set) were 2 incidences of pruritus and 1 incidence of dermal cyst. The graft necrosis and the 2 cases of pruritus considered related to ARTISS 4 IU (Slow Set) each had an equivalent AE with the exact start date and severity reported at a control wound where skin grafts were affixed with staples. Therefore, these events are most likely not related to ARTISS 4 IU (Slow Set), but instead are expected outcomes for any grafted wound regardless of the method of attachment.

Overall, the data collected and analyzed during this study demonstrated that ARTISS 4 IU (Slow Set) is safe for the attachment of sheet skin grafts in subjects with deep partial thickness or full thickness burn wounds.

The ADRs and their frequencies are summarized in the table below:

System Organ Class	Adverse events (Preferred Term)	ARTISS 4 IU Number of events/ Number of patients treated
Skin and subcutaneous tissue disorders	Dermal cyst	1/138
	Pruritus	2/138
Injury poisoning and procedural complications	Skin graft failure	5/138

The following ADRs have been reported from clinical trials where ARTISS was used for adherence of skin flaps in facial rhytidectomy surgeries (*see Part II Clinical Trials, trial numbers 550703 and 550901*). Both studies had a split-face design in which one side of the face was treated with ARTISS as an adjunct to standard of care (SoC) and the other side received SoC only, which was closure of the flap with staples and suturing. Adverse events that occurred on the face at an overall frequency greater than or equal to 1% are shown in the table below.

System Organ Class (SOC)	Preferred MedDRA Term	ARTISS Side of Face N (%)*	Standard of Care Side of Face N (%)*	Both Sides of the Face N (%)*
General disorders and administration site conditions	Oedema	0	1 (0.83)	3 (2.5)
Injury, poisoning and procedural complications	Post procedural haematoma	1 (0.83)	11 (9.17)	NA**
	Seroma	4 (3.33)	6 (5.00)	NA**
	Wound dehiscence	1 (0.83)	1 (0.83)	0

* Percent is based on total number of subjects in safety analysis set: 120.

** NA = Not applicable; Hematoma/seromas occurring simultaneously on both sides of face were reported as two separate AEs.

Three subjects experienced serious adverse events. Two were local: wound abscess on the ARTISS treated side of the face that was recognized on postoperative day 14 and treated by operative incision and drainage; and a case of basal cell carcinoma on the SoC side of the face. A third subject experienced dehydration on the second postoperative day.

Post-Market Adverse Drug Reactions

Vascular disorders:

Air embolism*

- * as with other fibrin sealants, life-threatening/fatal air or gas embolism has occurred when using devices with pressurized air or gas; this event appears to be related to an inappropriate use of the spray device (e.g., at higher than recommended pressure and in close proximity to the tissue surface)

Manifestations of hypersensitivity include application site irritation, chest discomfort, chills, headache, lethargy, restlessness, and vomiting.

There have been rare reports of fatalities following the misadministration of topical thrombin.

Because these reactions are reported voluntarily and the population is of uncertain size, it is not always possible to reliably estimate the frequency of these reactions.

DRUG INTERACTIONS

Overview

No formal interaction studies have been performed.¹ Drug Interactions are not known. ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) can even be applied in fully heparinised patients (e.g. extracorporeal circulation).

Incompatibilities

Solutions containing alcohol, iodine or heavy metals will interfere with the product's performance due to denaturation of proteins or other mechanisms. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of ARTISS.

Oxidized cellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials.

ARTISS must not be mixed with other medicinal products.

DOSAGE AND ADMINISTRATION

ARTISS 4 IU (Slow Set) (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) is available as frozen solutions for thawing.

ARTISS consists of a pre-filled double-chamber syringe containing Sealer Protein-Aprotinin Solution and Thrombin-Calcium Chloride Solution. ARTISS is available in 2, 4 and 10 mL pack sizes.

Dosing Considerations

For topical use only – do not inject.

Dry the site of application. Prior to applying ARTISS the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction

¹ No interactions have been identified from clinical trials, current medical/scientific literature, and safety reports.

devices). Do not use pressurized air or gas for drying the site.

Recommended Dose and Dosage Adjustment

Application of the product must be individualized to the patient by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.2-12 mL. For some procedures (e.g. the sealing of large burned surfaces), larger volumes may be required.

The initial amount of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary. However, avoid re-application of ARTISS to a pre-existing polymerized ARTISS layer as ARTISS may not adhere firmly to a polymerized layer.

It is recommended that the initial application cover the entire intended application area.

The skin graft should be attached to the wound bed immediately after ARTISS has been applied. The surgeon has up to 60 seconds to manipulate and position the graft prior to polymerization.

After the flap or graft has been positioned, hold in the desired position by gentle compression for at least 3 minutes to ensure ARTISS sets properly and the flap or graft adheres firmly to the underlying tissue.

The amount of ARTISS to be applied depends on the size of the surface to be covered. The approximate surface areas covered by each package size of ARTISS are listed in the following table:

Area to be sealed (cannula, catheter)	Area to be sealed using compressed gas (spray application)	Required package size of ARTISS
8 cm ²	25-100 cm ²	2 mL
16 cm ²	50-200 cm ²	4 mL
40 cm ²	125-500 cm ²	10 mL

Administration

Various methods can be used to simultaneously apply the two components of ARTISS:

- a) using application cannula contained in DUO Set
- b) using Spray Set and EASYSPRAY
- c) using DUPLOCATH Application Catheters or other accessories provided by Baxter

Preparation of ARTISS

Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

Do not remove the protective syringe cap until thawing is complete and application tip is ready to be attached.

Room Temperature Thawing

Approximate thawing times when using this method are:

Thawing Times at Room Temperature	Pack Size (In Pouches)
60 minutes	2 mL
110 minutes	4 mL
160 minutes	10 mL

Unopened pouches of ARTISS 4 IU (Slow Set), thawed at room temperature, may be stored for up to 7 days at room temperature (15°C to 25°C) after removal from the freezer.

ARTISS may be thawed under controlled conditions using one of the three following options:

Option 1 – Thawing on the sterile field using a Sterile Water Bath:

33°C to 37°C sterile water bath - transfer double-chamber syringe set and the inner pouch to the sterile field, remove the double-chamber syringe with pre-filled syringes from inner pouch and place directly into sterile water bath. Ensure the double-chamber syringe is completely immersed under the water.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Sterile Water Bath (Pouches Removed)
2 mL	5 minutes
4 mL	5 minutes
10 mL	12 minutes

Option 2 – Thawing off the sterile field using a Water Bath:

33°C to 37°C non-sterile water bath, double-chamber syringe in two pouches - maintain the double-chamber syringe set in both pouches and place into a water bath off the sterile field for appropriate time. Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch and pre-filled syringes onto the sterile field.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Non-Sterile Water Bath (In Pouches)
2 mL	30 minutes
4 mL	40 minutes
10 mL	80 minutes

Option 3 – Thawing off the sterile field using an Incubator:

Incubator (33°C to 37°C) in pouches – maintain the -pre-filled syringe in both pouches and place into an incubator for appropriate time. Remove from incubator after thawing and transfer inner pouch and pre-filled syringes onto the sterile field.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Incubator (In Pouches)
2 mL	40 minutes
4 mL	85 minutes
10 mL	105 minutes

NOTE:

After thawing, the product must not be refrigerated, refrozen or be exposed to temperatures above 37°C.

Keep the product at 33°C to 37°C until needed.

The product must be used within 12 hours after warming to 33°C to 37°C or removal from original pouches.

Method of Application

Application Considerations

See *WARNINGS AND PRECAUTIONS*, General and Application Precautions.

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

The setting rate depends on the concentration of the human Thrombin as contained in the Thrombin-Calcium Chloride solution used. The ARTISS Thrombin component is provided in a

4 IU/mL concentration (ARTISS 4 IU, Slow Set). A 500 IU/mL Thrombin concentration is also available and marketed as TISSEEL 500 IU, Fast Set.

Prior to application, ARTISS must be warmed to 33°C to 37°C. ARTISS must not be exposed to temperatures above 37°C and must not be microwaved.

The sealer protein and the thrombin solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Inspect products for particulate matter and discoloration prior to application.

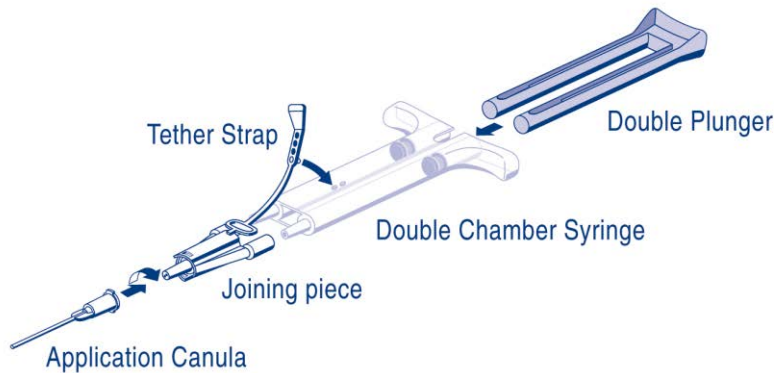
Before application of ARTISS, ensure that parts of the body outside the desired application area are sufficiently covered to prevent tissue adhesion at undesired sites.

- Prior to applying ARTISS the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction). Apply ARTISS as a thin layer. The initial amount of the product to be applied should be sufficient to entirely cover the intended application area.
- If ARTISS does not fully adhere to tissue and bleeding continues, remove ARTISS clot and repeat application.
- Ensure that the two components are quickly and thoroughly mixed, which is essential for ARTISS to gain the optimum strength.
- The Spray Set is particularly suitable for spraying of larger areas.
- In operation sites where access is difficult ARTISS can be applied using DUPLOCATH Application Catheters.
- The cannulas included with the DUO SET System may be used for small wounds or for edges of a skin graft that did not adhere to the wound bed.
- The skin graft should be attached to the wound bed immediately after ARTISS has been applied. With the use of ARTISS 4 IU/mL, approximately one minute is allowed for approximating the tissues to be glued. Hold in place for three minutes.
- Once turbid, ARTISS can no longer be manipulated.
- Solidified Sealant reaches its ultimate strength after about two hours (70% after about ten minutes).

a) Simultaneous Application using application cannula contained in DUO Set:

i) Administration using DUO Set

- For application, the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution has to be connected to a joining piece and an application cannula.



Operating Instructions:

- Remove the cap covering the nozzles of the double-chamber syringe.
- Connect the nozzles of the double-chamber syringe to the joining piece ensuring that they are firmly fixed. Secure the joining piece by fastening the tether strap to the double-chamber syringe. 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 cannula onto the joining piece.
- Fit the double plunger to the end of the syringe chamber.
- Do not expel the air remaining inside the joining piece or application cannula until you start actual application as the aperture of the cannula may clog otherwise
- Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed

If application of the fibrin sealant components is interrupted, clogging may occur in the cannula. To resume application, replace the application cannula with a new one. If the apertures of the joining piece are clogged, use the spare joining piece provided in the Duo Set.

b) Simultaneous Application Using Spray Set and EASYSPRAY:

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

- Any application of air or pressurized gas is associated with a potential risk of air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening.
- ARTISS must be sprayed only onto application sites that are visible.
- ARTISS must not be applied intravascularly. (See *WARNINGS AND PRECAUTIONS*)

Note: For operation instructions please refer to the Instructions for Use provided together with Spray Set and EASYSPRAY.



The Spray Set is particularly suitable for spraying of larger areas, e.g. to control oozing of parenchymatous organs or to adhere skin grafts. The two components are sprayed simultaneously using sterile propellant gas via EASYSpray, and the volume of the Solutions ejected is controlled with the DUO Set plunger. Limit the gas pressure to a maximum of 2 bars and spray at a minimum distance of 10 cm. Only use application devices licensed for the administration of ARTISS.

c) Simultaneous Application Using DUPLOCATH Application Catheters or other accessories provided by Baxter:

In operation sites where access is difficult ARTISS can be applied using DUPLOCATH Application Catheters.

Note: For operation instructions please refer to the Instructions for Use provided together with DUPLOCATH Application Catheter 25.

In case of using other accessories provided by Baxter, please refer to the operating instructions contained in the Instructions for Use for the particular accessory.

Gluing of Tissue

After the two components have been applied, approximate the wound areas. Fix or hold the glued parts in the desired position for three to five minutes to ensure that the setting Sealant adheres firmly to the surrounding tissue. Solidified Sealant reaches its ultimate strength after about two hours (70% after about ten minutes).

OVERDOSAGE

As the product is actively used by the surgeon, overdose is very unlikely to occur. ARTISS is only to be used by a physician in a hospital setting.

Only a thin layer of ARTISS should be applied to avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant. Excessive thickness of the fibrin layer may negatively interfere with the product's efficacy and the wound healing process (See *DOSAGE AND ADMINISTRATION* and *WARNINGS AND PRECAUTIONS*).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) is a tissue glue with sealing, hemostyptic and gluing properties, which does not interfere with but may enhance wound healing.

The action of ARTISS simulates key features of the physiological process of wound closure. A highly concentrated fibrinogen Aprotinin solution, which among other ingredients contains Factor XIII co-fractionated from the plasma, and a solution of thrombin and calcium chloride are applied to the wound area, where the mixture coagulates. The presence of Factor XIII causes the fibrin to crosslink, which gives the coagulum additional resilience. Aprotinin prevents premature degradation of the clot.

Spray application of ARTISS over the wound bed provides full surface adherence of grafts and skin flaps. Full surface adherence minimizes areas of dead space between the wound bed and applied tissues. Elimination of dead space prevents shear irritation upon movement as well as reduces the void space under the skin that can host fluid build-up.

Pharmacodynamics

Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin. Part of the thrombin is adsorbed by the fibrin, and any excess thrombin is inactivated by protease inhibitors in the blood.

Fibrinolysis Inhibitor, Aprotinin, is a polyvalent protease inhibitor that prevents premature degradation of fibrin. Free Aprotinin has a half-life ($t_{1/2}$) of approx. 0.82 and is eliminated by the kidney. Preclinical studies with different fibrin sealant preparations simulating the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of Aprotinin in the product formulation increases resistance of the fibrin sealant clot to degradation in a fibrinolytic environment.

Pharmacokinetics

ARTISS is intended for local application only, therefore systemic exposure or distribution to

other organs or tissues is not expected and pharmacokinetic studies were not conducted.

STORAGE AND STABILITY

When stored at $\leq -20^{\circ}\text{C}$ ($\leq -4^{\circ}\text{F}$), ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated), in pre-filled syringes, is stable until the expiry date indicated on the label.

Room Temperature Storage: Unopened pouches, thawed at room temperature, may be stored for up to 7 days at room temperature (15°C to 25°C) after removal from the freezer.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) is available as frozen solutions for thawing.

Strength	Volume (Total)	ARTISS
4 IU/mL	2 mL	1.0 mL/ 2.0 mL/ 5.0 mL of sterile frozen ARTISS Sealer Protein (Human)-Aprotinin Solution 1.0 mL/ 2.0 mL/ 5.0 mL of sterile frozen Thrombin (Human) – Calcium Chloride Solution
	4 mL	
	10 mL	

ARTISS also contains DUO Set, the sterile accessory devices consisting of 1 plunger, 2 joining pieces and 4 application cannulas.

See the following *Accessories* Section for more accessories for use with ARTISS.

Composition

ARTISS 4 IU consists of a double-chamber syringe containing Sealer Protein-Aprotinin (synthetic) Solution (syringe body 1) and Thrombin-Calcium Chloride Solution (syringe body 2).

	Component	Amount
1	Sealer Protein (Human)-Aprotinin Solution, sterile, contains:	
	- Total protein	96-125 mg/mL
	- Factor XIII	0.6-10 U/mL**

	- Fibrinogen (Clottable Protein)	72-110 mg/mL
	- Plasmafibrinectin (CIG)*	2-9 mg/mL
	- Plasminogen*	40 – 120 µg/mL
	- Aprotinin (synthetic) Solution, sterile	3,000 KIU/mL***
2	Thrombin (Human)-Calcium Chloride Solution, sterile, contains:	
	Thrombin (Human)	2.5 - 6.5 IU/mL****
	Calcium Chloride Solution, sterile	36 - 44 µmol/mL

* Development data, not tested at the Final Product level

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

*** 30 Kallidinogenase Inactivator Units (KIU) correspond to 1 FIP-Unit².

**** One International Unit (IU) of Thrombin is defined as the activity contained in 0.0853 mg of the First International Standard of Human Thrombin³.

Nonmedicinal ingredients in the Sealer Protein-Aprotinin solution are human albumin, niacinamide and water for injection (WFI). Nonmedicinal ingredients in the Thrombin-Calcium Chloride solution are human albumin, sodium chloride and water for injection (WFI). Sodium Hydroxide and Hydrochloric Acid are used to adjust the pH in both solutions.

All plasma units used for manufacture are ALT tested and non-reactive in tests for Hbs-antigen and antibodies to HCV, HIV-1 and HIV-2. Before further processing all individual plasma donations are subjected to an inventory hold for a possible look-back of plasma donations suspected of infection. All plasma units are tested by HIQ-PCR = Hyland Immuno Quality Assured Polymerase Chain Reaction.

ACCESSORIES

The following are some accessories for use with ARTISS. A complete list of accessories can be obtained from a Baxter representative. When using these devices, strictly follow the Instructions for Use of the devices.

FIBRINOTHERM	Combined Heating and Stirring Device
EASYSpray	Propellant gas control unit, manometer, reducing valve, and pressure tube.
Spray Set (sterile, disposable)	Disposable set consisting of sterile filter with connection tube, sensing line and a spray head.
DUPLOCATH 25 Application Catheter	Length: approximately 25 cm (10") Diameter: approximately 5 french (approx. 0.17 cm) Radiopaque. Sterile. Disposable.

Alternative reconstitution accessories are available for ARTISS.

2. PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

See PART I – DESCRIPTION and PART II – DETAILED PHARMACOLOGY Sections.

Product Characteristics

See PART I – DESCRIPTION and PART II – DETAILED PHARMACOLOGY Sections.

Viral Inactivation

ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses (see DETAILED PHARMACOLGY), by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses in the course of the manufacture.

The manufacturing procedure for ARTISS includes processing steps designed to further reduce the risk of viral transmission. In particular, vapor heating and solvent/detergent treatment processes are included in the manufacturing of Sealer Protein Concentrate and Thrombin. In addition the reduction factors as associated with DEAE-Sephadex Batch Chromatography and Ion Exchange Chromatography of the Thrombin drug substance purification were investigated. Validation studies were conducted using samples drawn from manufacturing intermediates for each of the two human plasma derived components. These samples were spiked with stock virus suspensions of known titers followed by further processing under conditions equivalent to those in the respective manufacturing steps.

The virus reduction factors (expressed as \log_{10}) of independent manufacturing steps were as follows for each of the viruses tested:

Reduction Factors for Virus Removal and/or Inactivation Sealer Protein Component						
Manufacturing Step	Mean Reduction Factors [\log_{10}] of Virus Tested*					
	HIV-1	HAV	BVDV	PRV	MMV	B19V
Early Manufacturing Steps	n.d.	n.d.	n.d.	n.d.	2.7**	3.4**
					2.3**	
Solvent/Detergent Treatment	>5.3	n.d.	>5.7	>5.9	n.d.	n.d.
Vapor Heat Treatment	>5.5	>5.6	>5.7	>6.7	1.2	1.0
Overall Reduction Factor (ORF)	>10.8	>5.6	>11.4	>12.6	3.5	3.3
Reduction Factors for Virus Removal and/or Inactivation Thrombin Component						
Manufacturing Step	Mean Reduction Factors [\log_{10}] of Virus Tested*					
	HIV-1	HAV	BVDV	PRV	MMV	B19V
Removal of Thrombin precursor protein from Cryosupernatant	3.2	1.5	1.8	2.5	1.2	1.7
Vapor Heat Treatment	>5.5	>4.9	>5.3	>6.7	1.0	>4
Solvent/Detergent Treatment	>5.3	n.d.	>5.5	>6.4	n.d.	n.d.
Ion Exchange Chromatography	n.d.	n.d.	n.d.	n.d.	3.6	n.d.
Overall Reduction Factor (ORF)	>14.0	>6.4	>12.6	>15.6	5.8	>5.7

n.d. = not determined

* The mean RF of all runs was calculated. E.g. when two runs were performed in study A and one run in study B for HIV-1, then the mean of the three RF's was calculated and listed in the table.

** As a conservative value for general and robust Parvovirus reduction capacity in steps 1 to 8, 2.3 logs were calculated from MMV and B19V reduction factors (omitting the higher B19V reduction factor). For calculation of and rationale behind this value, see further above in the section where the corresponding study is discussed. For calculation of virus-specific overall reduction factors, however, only virus-specific individual reduction factors were considered.

HIV-1: Human immunodeficiency virus 1; **HAV:** Hepatitis A virus; **BVDV:** Bovine viral diarrhea virus, a model for Hepatitis C virus; **PRV:** Pseudorabies virus, a model for enveloped DNA viruses, among those Hepatitis B virus; **MMV:** Mice minute virus, a model for Human Parvovirus B19, **B19V:** Human Parvovirus B19.

CLINICAL TRIALS

Numerous clinical studies investigating the safety and efficacy of the product as a hemostyptic and biodegradable tissue glue in various fields of surgery have been performed. A number of these were controlled studies in fields including orthopedic surgery, abdominal surgery, urology, and cardiovascular surgery. The cardiovascular safety study using the heat treated product has shown that Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated transmits neither hepatitis viruses nor HIV. Pre-clinical studies have shown that the vapor treated product is at least as effective as the heat treated product. In a clinical study, TISSEEL 500 IU (Fast Set) was shown to be non-inferior to an earlier formulation of the product, TISSEEL VH (predecessor product) and both products were shown not to transmit hepatitis, HIV or P19B.

Use of ARTISS has invariably shown superior results in the groups treated as against the untreated controls who underwent the same types of surgery. These results were attributable to an improved hemostasis and, therefore, reduced blood loss, a tighter sealing of sutures preventing leakages or a fast and uncomplicated healing of the surgical wound.

In none of the studies have systemic side-effects been seen nor has any product related transmission of viral hepatitis or HIV occurred in any of the patients treated.

Burns (grafts) - Study 550201:

ARTISS 4 IU was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomized, controlled, multicenter clinical study. In each of the 138 patients, two comparable test sites were identified. In one test site the skin graft was fixed with ARTISS 4 IU in the other test site the graft was fixed with staples (control). ARTISS 4 IU proved to be non-inferior to staples with respect to the primary efficacy endpoint, complete wound closure at Day 28 using a one-sided 97.5% confidence interval on the difference in the proportion of test sites successfully treated. Wound closure, defined as full coverage of the wound with a contiguous layer of viable epithelium, was evaluated by a blinded evaluator panel from Day 28 photographs. Results are given in the table below:

Test sites with complete wound closure on Day 28		
	ARTISS 4 IU	Staples (control)
Intent to Treat Analysis	55 of 127 (43.3%)	47 of 127 (37.0%)
Per Protocol Analysis	48 of 106 (45.3%)	42 of 106 (39.6%)

With respect to secondary endpoints, ARTISS 4 IU showed a significantly lower incidence and size of hematoma/seroma on Day 1 ($p < 0.0001$ for incidence as well as size). Incidence and area of engraftment on Day 5 and wound closure on Day 14, as well as area of wound closure on Day 28 were not different.

ARTISS 4 IU was also superior to staples with respect to patient satisfaction ($p < 0.0001$) and patients experienced significantly less anxiety about pain with ARTISS VH S/D 4 IU than with staples ($p < 0.0001$). Moreover, ARTISS VH S/D 4 IU was significantly superior to staples with respect to the investigator's assessment of quality of graft adherence, preference of fixation method and satisfaction with graft fixation, overall quality of healing and overall rate of healing ($p < 0.0001$).

Pediatrics (1.1 – 16 years of age) or (<16 years of age):

In this Phase 3 clinical study ARTISS 4 IU was used in 35 pediatric patients aged 1.1 to 16 years to affix skin grafts to burn wounds. Eighteen of these patients were less than or equal to 6 years old. Efficacy and safety in these pediatric patients was not different from an adult population.

Facial Rhytidectomy (flaps) - Studies 550703 and 550901:

ARTISS was investigated for adherence of skin flaps in facial rhytidectomy surgeries in two prospective, randomized, controlled, multicenter clinical studies. The combined study population consisted of 120 subjects between 40 and 71 years of age; 113 (94.2%) of the subjects were female and 7 (5.8%) were male. Both studies had a split-face design in which one side of the face was treated with ARTISS as an adjuvant to standard of care (SoC) and the other side received SoC (sutures or staples) alone; therefore each subject participated in both arms (ARTISS and SoC). In both the Phase 2 and Phase 3 studies, a standardized drain was placed in each side of the face prior to the flap closure and drainage volume from both sides of the face from all subjects was used to compare adherence.

The endpoints analyzed for the 2 studies are:

- Drainage volumes at 24 h post operatively, for each side of the face
- Occurrence of hematoma and seroma

Drainage Volume Comparison at 24 h Post Operative			
Clinical Study	Mean ± SD Drainage (mL) ARTISS Side of the Face	Mean ± SD Drainage (mL) SoC Side of the Face	p-Value
Phase 2 (Study 550703) 45 subjects	11.5 ± 13.7	26.8 ± 24.0	< 0.0001
Phase 3 (Study 550901) 75 subjects	7.7 ± 7.4	20.0 ± 11.3	< 0.0001

An integrated analysis of the occurrence of hematoma/seroma in all 120 subjects across two studies was performed. A comparison was made of the proportion of subjects experiencing a hematoma/seroma exclusively on the ARTISS-treated side of the face or on the SoC side of the face. The difference was statistically significant with 95% CI = 0.035 – 0.172, p <0.05.

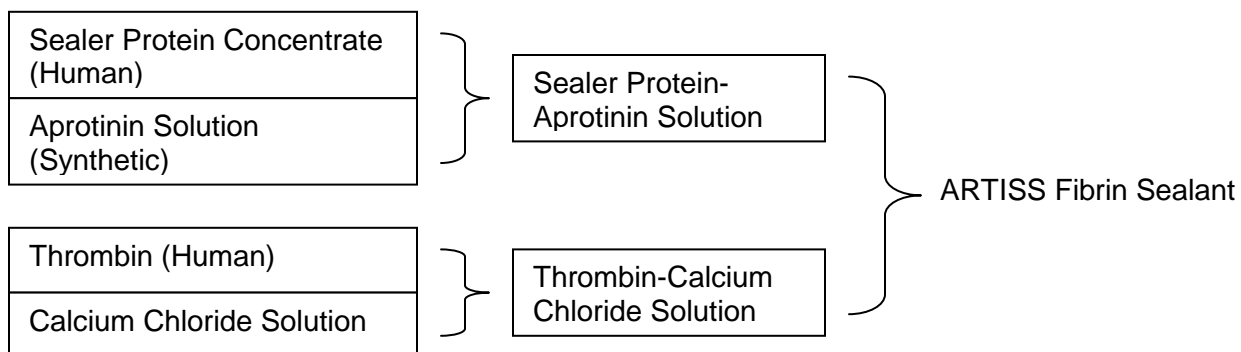
Occurrence of Hematoma / Seroma			
ARTISS n (%)	SoC n (%)	Both Sides of Face n (%)	Total n (%)
2 (1.7)	14 (11.7)	3 (2.5)	19 (15.8)

Geriatrics (> 65 years of age):

Clinical studies conducted with ARTISS 4 IU for adherence of skin flaps in facial rhytidectomy surgeries included 13 subjects aged 65 to 71 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DETAILED PHARMACOLOGY

ARTISS is filled in a double-chamber syringe, which is stored in a deep frozen condition: Sealer Protein Concentrate-Aprotinin (syringe chamber 1) and Thrombin-Calcium Chloride Solution (syringe chamber 2).



The two components are mixed either immediately before application to the recipient surface or in situ using one of the methods described under Application. The Sealer Protein / Thrombin Solution, after mixing, is a viscous solution adhering to wound surfaces and quickly sets to form a white, rubberlike mass, which continues to gain in strength within two hours following application. This process is made use of to achieve hemostasis, and to seal or glue tissue.

In this manner, the need for sutures may be reduced, although not totally eliminated. The time until Sealant sets can be used to approximate wound edges, to provide optimum conditions for healing. In the course of wound healing, Sealant is completely absorbed⁴.

Fibrin Sealant is a two-component biological sealant produced from pooled human plasma. As for all plasma products, the following measures are implemented to ensure the safety of the product from the potential presence of pathogenic viruses in human plasma:

- Donor selection
- Donation testing of single donations and also at the mini-pool and manufacturing pool level
- The use of PCR assay system (PCR) for release of plasma pools
- Effective virus inactivation/removal steps integrated into the manufacturing process including validation

Each plasma donation is tested for infectious markers for human immunodeficiency virus, types 1 and 2 (HIV-1/-2), hepatitis C virus (HCV) and hepatitis B surface antigen (HbsAg) The criteria for release of each single plasma donation for further manufacturing are as follows:

- HIV-1 / HIV-2 antibody: non-reactive
- HbsAg: non-reactive
- HCV antibody: non-reactive

Each manufacturing plasma pool is tested and released for further manufacturing only when

- non-reactive for Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis A Virus (HAV) and Hepatitis B Virus (HBV) using Nucleic Acid Testing (NAT)
- Parvovirus B19 concentration not exceeding 10^4 IU / mL as measured by NAT

Plasma pool are tested using HIQ-PCR = Hyland Immuno Quality Assured Polymerase Chain Reaction. With the PCR method, in general 500 genome equivalents/mL of the above viruses can be determined reliably, with the actual sensitivity of HIQ-PCR being below that. Therefore all pools which have been tested and evaluated as being positive lead to exclusion from further processing.

The plasma safety precautions and virus inactivation/removal steps taken during the manufacture of TISSEEL VH S/D 500 IU are equivalent to those used for ARTISS 4 IU. During the pivotal clinical study of TISSEEL VH S/D 500 IU Fibrin Sealant there were zero confirmed seroconversions for HAV, HBV, HCV, HIV or B19V (Baxter clinical study 550003).

Although viral safety was not an endpoint in the other clinical studies, any issues concerning viral safety would have been detected and followed up in the process of AE reporting. No reports concerning viral transmission from any studies, involving Fibrin Sealant 4 IU (ARTISS) or 500 IU (TISSEEL) were received.

The therapeutic activities of ARTISS are hemostasis, gluing and sealing of tissue, and the support of wound healing.

Physiologically, the process of wound closure starts when a bleeding ceases. In places where injured blood vessels lie open, hemostatic plugs form of platelets and fibrin, which become more and more solid as other blood cells, particularly erythrocytes, are involved. Because the bleeding ceases, blood that has escaped into the wound bed earlier coagulates. In a next step fibrin in both the coagulated blood and hemostatic plug retracts, plasma is squeezed out, the blood vessels contract, and the wound area becomes smaller. As various cells begin to proliferate into the retracted blood coagula, wound healing sets in.

In developing Fibrin Sealant, this principle has at least partly been simulated by applying a highly concentrated fibrinogen solution, which also contains factor XIII as co-fractionated from the plasma, and a solution of thrombin and calcium chloride to the wound area, where the mix coagulates. Since the Sealant does not contain thrombocytes, the clotted fibrin does not

appreciably retract. When the mixture is applied, however, the fibrin concentration in the coagulum is the same as or higher than that of a retracted hemostatic plug. To preserve the coagulum until the wound healing has reached a stage where it is no longer required, the Sealant has been designed to contain a fibrinolysis inhibitor.

The fibrin in the Sealant adheres perfectly to the wound edges guaranteeing adequate sealing effect. Similar to the hemostatic plug, wound healing is promoted by the fibrin applied. Combined application of Sealant with a mixture of autologous or homologous spongiosa provides excellent plugging material for bone defects. Using adequate technique, ARTISS is also an excellent tool in sealing autologous or homologous cartilage and bone.

ARTISS and all of its components have not been observed to affect systemic circulation, respiration, or the central nervous system. This is attributable to both the fact that only minimal quantities of each single component are applied compared to their use for other indications, and the fact that ARTISS becomes only locally effective.

The mechanism underlying solidification of tissue and persistence of a solidified clot have been investigated in numerous studies.

As a biologic material, Fibrin Sealant becomes completely absorbed at a rate which depends both on the fibrinolytic activity of the surrounding tissue and the quantity of Fibrinolysis Inhibitor added. In the course of wound healing the Sealant clot is gradually replaced by ingrowing tissue, Thrombin is inactivated by the physiological protease inhibitors, Calcium Chloride is subjected to the calcium and chloride catabolism of the organism, and Aprotinin and its metabolites are eliminated by the kidney.

TOXICOLOGY

The studies performed with TISSEEL containing 500 IU thrombin concentration confirm the safety profile of ARTISS 4 IU, as the low concentration of thrombin (4 IU) is not expected to cause any further toxicity than the 500 IU thrombin concentration.

The local application of TISSEEL / ARTISS (Fibrin Sealant (Human), Vapor Heated, Solvent/Detergent Treated) underlines the importance of histological studies for toxicology data. Accordingly, histologies have been performed on various species in tissues ranging from skin, vessels, nerves, tendons, organ tissue to bone.

In vivo toxicology studies indicated no acute toxicity and normal local tolerance reactions of TISSEEL Frozen² with bovine or synthetic Aprotinin in rats and rabbits, respectively. Furthermore, no difference between synthetic and bovine Aprotinin for single-dose toxicity after intravenous application could be detected in mice and rats and synthetic Aprotinin was well

² The composition of TISSEEL frozen, thawed, is identical to the composition of the reconstituted TISSEEL freeze-dried.

tolerated in rabbits.

No skin sensitizing potential of synthetic Aprotinin was shown in a Guinea Pig Maximization Test.

In vitro, no differences were found between TISSEEL 500 IU Frozen with bovine or synthetic Aprotinin and the predecessor product TISSEEL VH 500 IU lyophilized Kit with respect to cellular compatibility, or mutagenicity.

Synthetic Aprotinin was non-mutagenic an Ames test.

Cellular compatibility was confirmed in an additional *in vitro* study comparing both TISSEEL preparations (frozen and lyophilized) and the predecessor product TISSEEL VH (lyophilized) Kit.

In summary, presented *in vitro* and *in vivo* data support the equivalence of TISSEEL (frozen and lyophilized) with the predecessor product TISSEEL VH (lyophilized Kit). Moreover, it was shown that synthetic Aprotinin has no negative impact on the safety of the Fibrin Sealant.

Long-term animal studies to evaluate the carcinogenic potential of TISSEEL or studies to determine the effect of TISSEEL on fertility have not been performed.

On the following page the toxicology program is presented.

Toxicology program for Baxter Fibrin Sealants

Study Type	Route of Administration	Species	Test Article
Single-dose Toxicity	s.c.	Rat	TISSEEL (frozen)
Single-dose Toxicity	s.c.	Rabbit	TISSEEL (frozen)
Single-dose Toxicity	s.c.	Rat	TISSEEL s-apr (frozen)
Single-dose Toxicity	s.c.	Rabbit	TISSEEL s-apr (frozen)
Single-dose Toxicity	i.v.	Mouse	Synthetic Aprotinin
Single-dose Toxicity	i.v.	Rat	Synthetic Aprotinin
Genotoxicity	i.v.	<i>E. coli</i>	TISSEEL (frozen)
Genotoxicity	i.v.	<i>Salmonella typhimurium</i>	Synthetic Aprotinin
Local Tolerance	s.c. spongiosa blocks	Rat	TISSEEL (frozen)*
Local Tolerance	s.c. spongiosa blocks	Rabbit	TISSEEL (frozen)*
Local Tolerance	s.c. spongiosa blocks	Rat	TISSEEL s-apr (frozen)*
Local Tolerance	s.c. spongiosa blocks	Rabbit	TISSEEL s-apr (frozen)*
Local Tolerance	i.v., paravenous	Rabbit	Synthetic Aprotinin
Cytotoxicity	i.v.	Human lung fibroblasts	TISSEEL (frozen)
Cytotoxicity	i.v.	Human lung fibroblasts	TISSEEL (lyophilized)
Cytotoxicity	i.v.	Human lung fibroblasts	TISSEEL s-apr (frozen)
Skin Sensitization	intradermal, epicutan	Guinea pig	Synthetic Aprotinin

* Local tolerance studies using a subcutaneously implanted spongiosa block model were conducted with fibrin sealants diluted to a Thrombin concentration of 4 IU/mL.

3. PART III: CONSUMER INFORMATION

PATIENT COUNSELING INFORMATION

Because this product is made from human plasma, the physician should discuss the risks and benefits with the patient. Patient should be encouraged to consult with their physician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain).

REFERENCES

1. REDL H., SCHLAG G., DINGES H. P.: Methods of Fibrin Seal Application. Thorac. Cardiovasc. Surg. 30, 223–227 (1982)
2. HENNRICH N., BRÜMMER W.: 3. Bericht: Trypsin-Inhibitor. Pharm. Ind. 35, 272–273 (1973)
3. ROBERTSON I., GAFFNEY P. J., BANGHAM D. R.: Standard for human thrombin. Thrombos. Diathes. Haemorrh., Stuttgart 34, 3–18 (1975)
4. REDL H. et al.: Grundlagen der Fibrinklebung. In: Fibrinkleber in Orthopädie und Traumatologie 4. Heidelberger Orthopädie-Symposium, H. Cotta/A. Braun (Eds.), Georg Thieme Verlag: 18–21 (1982)
5. Validation of Virus Removal and Inactivation in the Course of the Manufacture of Sealant Protein Concentrate (Human) Vapor Heated (without Creatine) Using HIV-1, HAV, and Model Viruses
6. Validation of Virus Removal and Inactivation by DEAE-Adsorption, Lyophilization, and Vapor Heating in the Course of the Manufacture of Thrombin (Human) Vapor Heated, Using HIV-1, and Model Viruses
7. Validation of Virus Inactivation by Vapor Heating of Thrombin (Human) Using Hepatitis A Virus
8. A Study to Determine the Safety of Virus Inactivated Factor Concentrates in Hemophiliacs Naive to Blood Product Administration - International Factor Safety Study” Part II: Antihemophilic Factor/Factor VIII Concentrate (Human) IMMUNO, Vapor Heated (Evaluation as of February 23, 1994)
9. A Study to Determine the Safety of Virus Inactivated Factor Concentrates in Hemophiliacs Naive to Blood Product Administration - International Factor Safety Study” Part II: Factors VII and IX (Evaluation as of March 1, 1995).
10. Spontaneous Adverse Experience Reports: TISSUCOL/TISSEEL KIT, Two-Component Fibrin Sealant, Freeze Dried, Steam Treated (January 01, 1990 to December 31, 1995)