BAXTER

1. NAME OF THE MEDICINAL PRODUCT

ARTISS Solutions for Sealant
Deep frozen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARTISS is a two-component fibrin sealant made from pooled human plasma. The two components of ARTISS are formulated as two sterile, deep-frozen solutions.

Component 1:
Sealer Protein Solution

Human Fibrinogen (as clottable protein)	91 mg/ml[1] produced from the plasma of human donors
Aprotinin (synthetic)	3000 KIU/ml[2]

Component 2:
Thrombin Solution

Human Thrombin	4 IU/ml[3] produced from the plasma of human donors
Calcium Chloride	40 µmol/ml

[1] Contained in a total protein concentration of 95 – 125 mg/ml
[2] 1 EPU (European Pharmacopeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)
[3] Thrombin activity is calculated using the current WHO International Standard for Thrombin

1 prefilled double chamber syringe which contains Sealer Protein Solution (with Aprotinin), deep frozen 1 ml, 2ml or 5 ml, in one chamber and Thrombin Solution (with Calcium Chloride), deep frozen 1ml, 2 ml, 5 ml, in the other chamber results in 2 ml, 4 ml or 10 ml total volume of product ready for use.

After mixing	1 ml	2 ml	4 ml	10 ml
Component 1: Sealer protein solution				
Human Fibrinogen (as clottable protein)	45.5 mg	91 mg	182 mg	455 mg
Aprotinin (synthetic)	1,500 KIU	3,000 KIU	6,000 KIU	15,000 KIU
Component 2: Thrombin Solution				
Human Thrombin	2 IU	4 IU	8 IU	20 IU
Calcium Chloride	20 µmol	40 µmol	80 µmol	200 µmol

ARTISS contains Human Factor XIII co-purified with Human Fibrinogen in a range of 0.6 – 5 IU/ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Sealants
Deep-frozen
Colourless to pale yellow and clear to slightly turbid solutions

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARTISS is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and paediatric populations greater than or equal to 1 year of age.

ARTISS is indicated to adhere tissue flaps during facial rhytidectomy surgery (face-lift) in adults.

ARTISS is not indicated for haemostasis.

4.2 Posology and method of administration

ARTISS is intended for Hospital Use Only by suitably experienced physicians or surgeons.

Posology:
The amount of ARTISS to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualised 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, to any small areas that may have not been previously treated. However, avoid reapplication of ARTISS to a pre-existing polymerised ARTISS layer as ARTISS will not adhere to a polymerised layer.

As a guideline for the gluing of surfaces, 1 pack of ARTISS 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm^2.

When the fibrin sealant is applied by spray application the same quantity will be sufficient to coat an area of up to 100 cm^2, depending on the specific indication and the individual case.

For large surface areas, spray application is recommended. The required amount of ARTISS depends on the size of the surface to be covered. The approximate surface areas covered by each package size of ARTISS by spray application are:

Approximate area requiring tissue adherence	Required package size of ARTISS
100 cm^2	2 mL
200 cm^2	4 mL
500 cm^2	10 mL

This recommended amount applies to all age groups.

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 polymerisation.

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 graft or flap adheres firmly to the underlying tissue.

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

ARTISS has not been administered to patients > 65 years old in clinical trials.

Paediatric Population

Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method and route of administration

For epilesional (topical) use. Do not inject.

For subcutaneous use only. ARTISS is not recommended for laparoscopic surgery. See also section 4.4.

In order to ensure optimal safe use of ARTISS it should be sprayed using a pressure regulator device that delivers a maximum pressure of up to 2.0 bar (28.5 psi).

ARTISS must be sprayed only onto application sites that are visible.ARTISS should only be reconstituted and administered according to the instructions and with the devices recommended for this product (see section 6.6).

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

For spray application, see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure and length of applicator tips.

4.3 Contraindications

ARTISS is not indicated to replace skin sutures intended to close surgical wounds.

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

ARTISS must never be applied intravascularly. Such use has been associated with inadvertent intravascular injection, with thromboembolic complications. ARTISS should only be used topically.

Additionally, soft tissue injection of ARTISS carries the risk of an anaphylactic reaction and/or local tissue damage.

ARTISS is contraindicated in the case of hypersensitivity to the active substances or to any of the excipients listed in section 6.1. (see also section 4.4).

Spray application of ARTISS should not be used in endoscopic procedures. For laparoscopy, see section 4.4.

4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly. Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly. Soft tissue injection of ARTISS carries the risk of local tissue damage.

Caution must be used when applying fibrin sealant using pressurised gas.

Any application of pressurised gas is associated with a potential risk of air embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening.

- ARTISS must not be used with the Easy Spray / Spray Set system in enclosed body areas for serious safety reasons.
- Apply ARTISS as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.
- ARTISS must be sprayed only onto application sites that are visible.
- Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with ARTISS when sprayed in open wound surgery.
- When applying ARTISS using a spray device, the pressure should be within the range recommended by the spray device manufacturer. (see table in section 6.6 for pressures and distances).
- Spray application of ARTISS should only be done using the provided spray application accessories and the pressure should not exceed 2.0 bars. In the absence of a specific recommendation ARTISS should not be sprayed closer than 10-15 cm from the tissue surface.
- When spraying ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.
- ARTISS should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.
- ARTISS is not recommended for laparoscopic use.
- When using accessory tips with this product, the instructions for use of the tips should be followed.

ARTISS is not indicated for haemostasis and sealing in situations where a fast clotting of the sealant is required. Especially in cardiovascular procedures in which sealing of vascular anastomoses is intended ARTISS should not be used.

ARTISS is not indicated for use in neurosurgery and as a suture support for gastrointestinal anastomoses or vascular anastomoses as no data are available to support these indications.

Before administration of ARTISS care is to be taken that parts of the body outside the designated application area are sufficiently protected/covered to prevent tissue adhesion at undesired sites.

Oxycellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials (see section 6.2).

Polysorbates can cause skin allergy (e.g. rash, itching).

As with any protein-containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration must be discontinued immediately.

ARTISS contains aprotinin. Even in case of strict local application, there is a risk of anaphylactic reaction linked to the presence of aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records.

As synthetic aprotinin is structurally identical to bovine aprotinin the use of ARTISS in patients with allergies to bovine proteins should be carefully evaluated.

In the event of anaphylactic/anaphylactoid or severe hypersensitivity reactions, administration is to be discontinued. Remove any applied, polymerised product from the surgical site. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction. State-of-the-art emergency measures are to be taken.

In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from

human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., haemolytic anaemia).

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

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed with ARTISS.

Similar to comparable products or thrombin solutions, the product is denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

See section 4.4 or 6.2 for substances that can interfere with the product’s performance.

4.6 Fertility, Pregnancy and lactation

The safety of fibrin sealants/haemostatics for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Animal studies have also not been performed.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

See section 4.4 for information on Parvovirus B19 infection.

The effects of ARTISS on fertility have not been established.

4.7 Effects on ability to drive and use machines

There is no information of the effects of ARTISS on the ability to drive or operate an automobile or other heavy machinery.

4.8 Undesirable effects

Intravascular injection could lead to thromboembolic events and DIC and there is also a risk of anaphylactic reactions (see section 4.4).

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin (see section 4.4) or any other constituents of the product.

Even if a first treatment with ARTISS was well tolerated, a subsequent administration of ARTISS or systemic administration of aprotinin may result in severe anaphylactic reactions. Antibodies against components of fibrin sealant may rarely occur.

For safety with respect to transmissible agents, see section 4.4.

Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

The safety population comprised of a total of 298 subjects enrolled in the burn and rhytidectomy surgery trials. The data described in Table 1 reflects the exposure to ARTISS in 4 burn and rhytidectomy surgery trials.

Table 1
Trial Population Demographics

	Burn		**Rhytidectomy**	
Parameter	**Supporting Trial**	**Confirmatory Trial**	**Supporting Trial**	**Confirmatory Trial**
Sample size (N)	40	138	45	75
Gender **F (%) /** **M (%)**	 11 (27.5%) 29 (72.5%)	 44 (31.9%) 94 (68.1%)	 42 (93.3%) 3 (6.7%)	 71 (94.7%) 4 (5.3%)
Age Range (years)	6 – 55	1 – 63	43 – 70	40 – 71

Volume applied (Mean ± SD) (Range in mL)	2.9 ± 1.64 (Range: 1.0 – 10.8)	2.7 ± 1.9 (Range: 0.2 – 12.0)	2.32 ± 0.95 (Range: 0.80 – 4.0)	2.58 ± 1.17 (Range: 0.60 – 4.0)

Adverse reactions reported from these clinical studies are summarised in Table 2.

The ADRs and their frequencies are summarised below:
Common (≥1/100 to <1/10) Uncommon (≥1/1000 to <1/100)

Table 2
Clinical Trial Adverse Reactions

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**Dermal cyst** **Pruritus**	Uncommon Common
INJURY POISONING AND PROCEDURAL COMPLICATIONS	**Skin graft failure** **Seroma**	Common Common
VASCULAR DISORDERS	**Haematoma**	Common

Class Effects
Other adverse reactions associated with products of the fibrin sealant/haemostatic class are provided in the Table below, frequencies of those cannot be provided.

Table 3
Class Effects

System organ class (SOC)	Preferred MedDRA Term
Immune System Disorders	Hypersensitivity
	Anaphylactic reaction
Cardiac Disorders	Bradycardia
	Tachycardia
Vascular Disorders	Hypotension
	Haematoma
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea
Gastrointestinal Disorders	Nausea
Skin and subcutaneous tissue Disorders	Urticaria
	Flushing

General Disorders and Administration Site Conditions	Impaired Healing
	Oedema
	Pyrexia
Injury, poisoning and procedural complications	Seroma

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: local haemostatics, ATC code: B02BC; tissue adhesives, ATC code: V03A K

ARTISS can replace sutures or staples when used for fixation of skin grafts to burned or otherwise injured wound areas. ARTISS can be used as an adjunct to sutures or staples to adhere and seal skin flaps in cases where sutures/staples are expected to yield unsatisfactory results with respect to postoperative haematoma or seroma formation.

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for the conversion of fibrinogen and the crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by antifibrinolytics. Aprotinin is present in ARTISS as an antifibrinolytic to prevent premature degradation of the clot.

For efficacy, *in vivo* studies in an animal model closely imitating the situation in patients were used. ARTISS demonstrated efficacy regarding sealing autologous split skin grafts and mesh grafts.

Burns (grafts)
ARTISS was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomised, controlled, multicentre 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 in the other test site the graft was fixed with staples (control). ARTISS proved to be non-inferior to staples with respect to the primary efficacy endpoint, complete wound closure at Day 28 was

evaluated by a blinded evaluator panel from photographs. This was achieved in 55/127 patients (43.3%) treated with ARTISS and 47/127 patients (37%) treated with staples.

With respect to secondary endpoints, ARTISS showed a significantly lower incidence and size of haematoma/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 was also superior to staples with respect to patient satisfaction ($p < 0.0001$) and patients experienced significantly less anxiety about pain with ARTISS than with staples ($p < 0.0001$). Moreover, ARTISS 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 ($p < 0.0001$).

Thirty-seven (37) paediatric patients aged 1.1 to 18 years were evaluated in this trial. Eighteen (18) of these patients were 6 years old or younger. Dosage used in clinical trials was the same for paediatric and adult patients.

Facial Rhytidectomy (flaps)

The efficacy of ARTISS for adherence of skin flaps in facial rhytidectomy surgeries was evaluated in two prospective, randomised, controlled, multicentre clinical trial. Both the confirmatory trial (n=75) and supportive trial (n=45) utilized a split-face design in which 1 side of the face was treated with ARTISS as an adjunct to the standard of care (SoC) and the other side received SoC only, which was closure of the flap by means of staples and suturing only; therefore each subject participated in both arms (ARTISS and SoC).

Primary endpoint of the confirmatory trial conducted in 75 subjects was the total drainage volume collected from each side of the face at 24 h (±4 h) post surgery. Occurrence of haematoma and seroma on each side of the face, comparison of oedema between the 2 sides of the face, changes in skin sensitivity from baseline on each side of the face and subject preference were evaluated as secondary endpoints.

In both trials, 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 compared. Pressure dressings were not allowed.

The results for the primary endpoint of the confirmatory trial are presented in Table 4a below.

Table 4a
Drainage Volume Comparison at 24 h Post Operative in Confirmatory Trial

Clinical Trial (n=75)	Mean ± SD Drainage (mL)	Mean ± SD Drainage (mL)	p-Value

	ARTISS Side of the Face	SoC Side of the Face	
Confirmatory Trial	7.7 ± 7.4	20.0 ± 11.3	< 0.0001

A statistically significant difference in drainage volumes was observed, favouring the side of the face treated with ARTISS.

Drainage volumes at 24 h post operatively for each side of the face reported as secondary endpoint in the supporting trial are presented in Table 4b below.

Table 4b
Drainage Volume Comparison at 24 h Post Operative in Supporting Trial

Clinical Trial (n=45)	Mean ± SD Drainage (mL) ARTISS Side of the Face	Mean ± SD Drainage (mL) SoC Side of the Face
Confirmatory Trial	11.5 ± 13.7	26.8 ± 24.0

An integrated analysis of the occurrence of haematoma/seroma in all 120 subjects across two trials was performed. A comparison of the proportion of subjects experiencing a haematoma/seroma exclusively on the ARTISS-treated side or on the SoC side of the face is presented in Table 5 below.

Table 5
Occurrence of Haematoma/Seroma

Clinical Trial	**ARTISS n (%)**	**SoC n (%)**	**Both Side of Faces n (%)**	**Total n (%)**
Supporting Trial	0	9 (20%)	0	9 (20%)
Confirmatory Trial	2 (2.7%)	5 (6.7%)	3 (4%)	10 (13.3%)

5.2 Pharmacokinetic properties

ARTISS is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Pharmacokinetic studies in different species of laboratory animals were not conducted.

Fibrin sealants/ haemostatics are metabolised in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

No preclinical safety data are available for ARTISS (thrombin 4 IU/ml). Toxicity studies were done with Fibrin Sealants containing thrombin 500 IU/ml, as representative for products

containing thrombin 4 IU/ml. Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of Fibrin Sealant VH S/D (500 IU/ml). Fibrin Sealant VH S/D (500 IU/ml) also proved well tolerated in wound healing models in rats and rabbits, and in *in vitro* human fibroblast cultures.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component 1: Sealer Protein Solution
Human Albumin Solution
L-Histidine
Niacinamide
Polysorbate 80 (Tween 80)
Sodium Citrate Dihydrate
Water for Injections

Component 2: Thrombin Solution
Human Albumin Solution
Sodium Chloride
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Oxycellulose-containing preparations may reduce the efficacy of ARTISS and should not be used as carrier materials.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store and transport frozen (at ≤ -20°C) without interruption until preparation for use.

Keep the syringe in the outer carton in order to protect from light.

Unopened pouches, thawed at room temperature, may be stored for up to 14 days at room temperature (not exceeding +25°C).

Once thawed, do not refreeze or refrigerate.

6.5 Nature and contents of container

Content of package with PRIMA Syringe

> 1 ml, 2 ml or 5 ml sealer protein solution and 1 ml, 2 ml or 5 ml thrombin solution in a pre-filled single-use double chamber syringe (polypropylene) closed with a tip cap packed in two bags and one device set with 2 joining pieces and 4 application cannulas.

Or

Content of package with AST Syringe:

> 1 ml, 2 ml, or 5 ml of sealer protein solution and 1, 2 or 5 ml of Thrombin Solution in a pre-filled single-use double-chamber syringe (polypropylene) closed with a tip-cap packed in two bags, and one device set with one double syringe plunger, 2 joining pieces and 4 application cannulae.

Pack size of 1 (1 x 1 ml + 1 ml, 1 x 2 ml + 2 ml, 1 x 5 ml + 5 ml)

Both Sealer Protein Solution and Thrombin Solution are contained in a pre-filled single-use double-chamber syringe made of polypropylene.

Not all pack sizes may be marketed.

Other accessories for application of the product can be obtained from BAXTER.

6.6 Special precautions for disposal and other handling

General

Before the administration of ARTISS, cover allparts of the body outside the area to be treated in order to prevent tissue adhesion at undesired sites.

As a guideline for the gluing of surfaces, 1 pack of ARTISS 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm^2.

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

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

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

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

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

Do NOT use ARTISS until it is completely thawed and warmed to 33°C – 37°C.
Remove the protective cap of the syringe only when thawing and warming is complete.
For PRIMA syringe: To facilitate removal of the tip cap from the syringe, rock the tip cap by moving it backward and forward, then pull the protective cap off the syringe.

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

Instructions for Handling and Preparation

The inner bag and its contents are sterile unless the integrity of the outside package is compromised. Using sterile technique, transfer the sterile inner pouch and contents onto the sterile field.

The ready-to-use syringe may be thawed AND warmed using one of the following methods:

1. **Rapid thawing/warming (sterile water bath) – *Recommended method***
2. Thawing/warming in a non-sterile water bath
3. Thawing/warming in an incubator
4. The ready-to-use syringe may also be thawed and kept at room temperature (not above 25°C) for up to 14 days. Warming is required prior to use.

1. Rapid thawing/warming (sterile water bath) – Recommended method:

- It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. In order to monitor the specified temperature range, control the water temperature using a thermometer and change the water as necessary.

- When using a sterile water bath for thawing and warming, remove the pre-filled syringe from the bags before placing it in the sterile water bath.

Instructions:

Bring the inner bag into the sterile area, remove the ready-to-use syringe from the inner bag and place it directly in the sterile water bath. Ensure that the content of the ready-to-use syringe is completely immersed in the water.

Table 1: Minimum thawing and warming Times using a Sterile Water Bath

Pack Size	**Minimum Thawing/Warming Times 33°C to 37°C, Sterile Water Bath, Product without bags**	
	PRIMA Syringe	AST Syringe
2 ml	5 minutes	5 minutes
4 ml	5 minutes	5 minutes
10 ml	10 minutes	12 minutes

2) Thawing/warming in a non-sterile water bath

Instructions:

Leave the ready-to-use syringe inside both bags and place it in a water bath outside the sterile area for the appropriate length of time (see Table 2). Ensure that the bags remain immersed in the water during the entire thawing time. After thawing, remove the bags from the water bath, dry the outer bag and bring the inner bag with the ready-to-use syringe into the sterile area.

Table 2: Minimum thawing and warming times using a non-sterile water bath

Pack Size	**Minimum Thawing/Warming Times 33°C to 37°C, Non-sterile Water Bath Product in bags**	
	PRIMA Syringe	**AST Syringe**
2 ml	15 minutes	30 minutes
4 ml	20 minutes	40 minutes
10 ml	35 minutes	80 minutes

3) Thawing/warming in an incubator

Instructions:

Leave the ready-to-use syringe inside both bags and place it in an incubator outside the sterile area for the appropriate length of time (see Table 3). After thawing/warming, remove the bags from the incubator, remove the outer bag and bring the inner bag with the ready-to-use syringe into the sterile area.

Table 3: Minimum thawing and warming times in an incubator

Pack Size	**Minimum Thawing/Warming Times 33°C to 37°C, Incubator Product in bags**	
	PRIMA Syringe	**AST Syringe**
2 ml	40 minutes	40 minutes
4 ml	50 minutes	85 minutes
10 ml	90 minutes	105 minutes

4.. Thawing at Room Temperature (not above +25°C) BEFORE warming:

Instructions:

Leave the ready-to-use syringe inside both bags and thaw it at room temperature outside the sterile area for the appropriate length of time (see Table 4). Once thawed, in order to warm the product for use, warm it in the outer bag in an incubator. After thawing at room temperature, the maximum time the product can be kept (in bags) at room temperature is 14 days.

Table 4: Minimum thawing times at Room Temperature (= RT) outside of the sterile field and additional warming times in an incubator to 33°C to 37°C

Pack Size	**Minimum Thawing Times of product at room temperature (not above 25°C) followed by additional warming, prior to use, in an incubator at 33°C to a maximum of 37°C Product in bags**	
	PRIMA Syringe	**AST Syringe**

	Thawing at room temperature (not above 25°C)	**Warming in Incubator (33-37°C)**	**Thawing at room temperature (not above 25°C)**	**Warming in Incubator (33-37°C)**
2 ml	80 minutes	+11 minutes	60 minutes	+15 minutes
4 ml	90 minutes	+13 minutes	110 minutes	+25 minutes
10 ml	160 minutes	+25 minutes	160 minutes	+35 minutes

Stability after thawing

After **thawing and warming** (at temperatures between 33°C and 37°C, methods 1, 2 and 3), chemical and physical product stability has been demonstrated for 4 hours at 33°C to 37°C.

For product **thawed** at room temperature in the unopened bag (method 4), chemical and physical product stability has been demonstrated for 14 days at temperatures no more than 25°C. Warm to 33°C to 37°C immediately before use.

From a microbiological point of view, unless the method of opening/thawing precludes the risks of microbial contamination, the product should be used immediately after being warmed to 33°C to 37°C.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Do not re-freeze or refrigerate once thawing has been initiated.

Handling after thawing / before application

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

The sealer protein and the thrombin solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Before use, check the thawed product visually for particles, discoloration or other changes in its appearance. If one of the above occurs, dispose of the solutions.

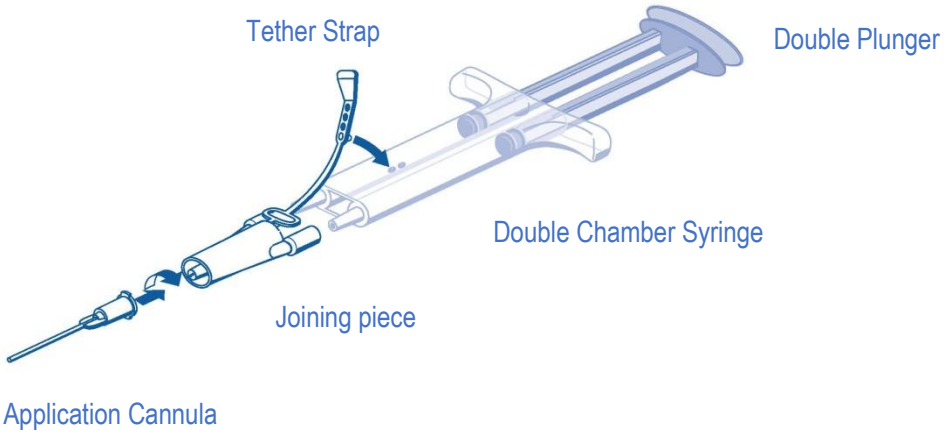
The thawed sealer protein solution should be liquid but slightly viscous. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (possibly due to an interruption of the cold storage chain or by overheating during warming). In this case, do NOT use ARTISS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

- Remove the syringe from the bags shortly before use.
- Use ARTISS only when it is thawed and warmed completely (liquid consistency).
- Remove the protective cap from the syringe immediately before application.
  For PRIMA syringe: To facilitate removal of the tip cap from the syringe, rock the tip cap by moving it backward and forward, then pull the protective cap off the syringe.

Non-Spray Administration with PRIMA Syringe:

For application, connect the double chamber ready-to-use syringe with the sealer protein solution and the thrombin solution to a joining piece and an application cannula – both are provided in the set with the application devices. The common plunger of the double chamber ready-to-use syringe ensures that equal volumes of the two sealant components are fed through the joining piece into the application cannula where they are blended and then applied.

Operating instructions for PRIMA Syringe:



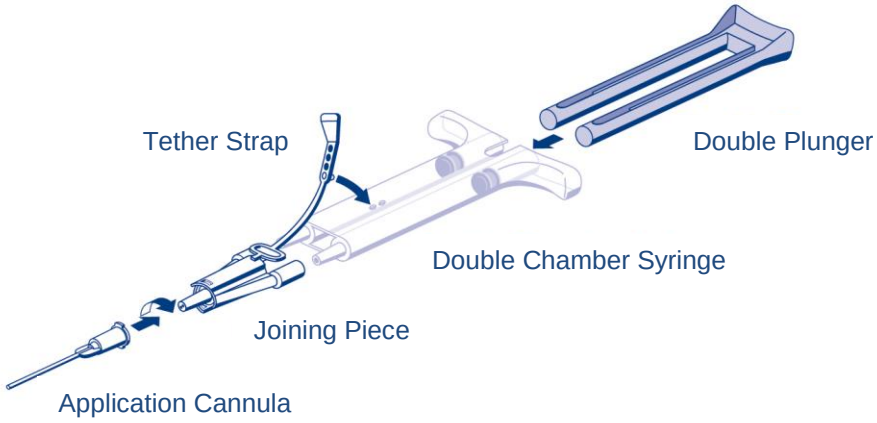
- Expel all air from the syringe prior to attaching any application device.
- Align the joining piece and tether to the side of the syringe with the tether strap hole.
- Connect the nozzles of the double chamber ready-to-use syringe to the joining piece, ensuring that they are firmly attached.
    - Secure the joining piece by fastening the tether strap to the double chamber ready-to-use syringe.
    - If the tether strap tears, use the spare joining piece provided in the kit.
    - If a spare joining piece is not available, the system can still be used if care is taken to ensure that the connection is secure and leak-proof.
    - Do NOT expel the air remaining inside the joining piece.
- Attach an application cannula on to the joining piece.
    - Do NOT expel the air remaining inside the joining piece and inside the application cannula until you start the actual application because this may clog the application cannula.

Or

Non-Spray Administration with AST Syringe:

For application, connect the double chamber ready-to-use syringe with the sealer protein solution and the thrombin solution to a joining piece and an application cannula – both are provided in the set with the application devices. The common plunger of the double chamber ready-to-use syringe, likewise provided in the set with the application devices, ensures that equal volumes of the two sealant components are fed through the joining piece into the application cannula where they are blended and then applied.

Operating instructions for AST Syringe:



- Expel all air from the syringe prior to attaching any application device.
- Align the joining piece and tether to the side of the syringe with the tether strap hole.
- Connect the nozzles of the double chamber ready-to-use syringe to the joining piece, ensuring that they are firmly attached.
    - Secure the joining piece by fastening the tether strap to the double chamber ready-to-use syringe.
    - If the tether strap tears, use the spare joining piece provided in the kit.
    - If a spare joining piece is not available, the system can still be used if care is taken to ensure that the connection is secure and leak-proof.

- Do NOT expel the air remaining inside the joining piece.

- Attach an application cannula on to the joining piece.
  - Do NOT expel the air remaining inside the joining piece and inside the application cannula until you start the actual application because this may clog the application cannula.

Administration

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

- Apply the mixed sealer protein - thrombin solution on to the recipient surface or on to the surfaces of the parts to be glued by slowly pressing on the back of the common plunger.
- In surgical procedures that require the use of minimal volumes of fibrin sealant, it is recommended to expel and discard the first few drops of product.
- After ARTISS has been applied, allow at least 3 minutes to achieve sufficient polymerization

Note: If application of the fibrin sealant components is interrupted, clogging may occur in the cannula. In this case, replace the application cannula with a new one immediately before application is resumed. If the openings of the joining piece are clogged, use the spare joining piece provided in the package.

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g. application to large or difficult-to-access areas. When using these application devices, strictly follow the Instructions for Use of the devices.

For further preparation instructions please refer to the responsible nurse or medical doctor.

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Spray application

The pressure regulatory should be used in accordance with the manufacturer's instructions.

When applying ARTISS using a spray device, be sure to use a pressure and a distance from tissue within the range recommended by the manufacturer as follows.

Recommended pressure, distance and devices for spray application of ARTISS					
	Spray set to be used	Applicator tips to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open wound surgery of subcutaneous tissue	Tisseel / Artiss Spray Set	n.a.	EasySpray	10 – 15 cm	1.5-2.0 bar (21.5-28.5 psi)
	Tisseel / Artiss Spray Set 10 pack	n.a.	EasySpray		

When spraying ARTISS, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism. (See section 4.2 and 4.4).

When using accessory tips with this product, the instructions for use of the tips should be followed.

Disposal

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

7 PRODUCT OWNER

Baxter AG
Industriestrasse 67
A-1221, Vienna, Austria

8 DATE OF REVISION OF TEXT

Apr 2021