SUMMARY OF PRODUCT CHARACTERISTICS

FOR

ARTISS, frozen

Master Text in Line with

Core SPC for Plasma Derived Fibrin Sealant / Hemostatic Products

(CPMP/BPWG/153/00)

1. NAME OF THE MEDICINAL PRODUCT

ARTISS Solutions for Sealant

Deep frozen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1:
Sealer Protein Solution
Human Fibrinogen (as clottable protein) 91 mg[1]/ml
Aprotinin (synthetic) 3000 KIU[2]/ml

Component 2:
Thrombin Solution
Human Thrombin 4 IU[3]/ml
Calcium Chloride 40 µmol/ml

1 prefilled double chamber syringe which contains Sealer Protein Solution (with Aprotinin), deep frozen <1 ml><2 ml><5 ml>, in one chamber and Thrombin Solution (with Calcium Chloride), deep frozen<1 ml><2 ml><5 ml>, in the other chamber results in <2 ml><4 ml><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

[1] Contained in a total protein concentration of 96 - 125 mg/ml
[2] 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)
[3] Thrombin activity is calculated using the current WHO International Standard for Thrombin.

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

Solutions for Sealant

Deep frozen

Colourless to pale yellow and clear to slightly turbid solutions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARTISS is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples (see 5.1). In addition, ARTISS is indicated as an adjunct to hemostasis on subcutaneous tissue surfaces.

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

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.

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.

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, or of the individual components, should be applied.

Method and route of administration

For epilesional use.

Prepare the solution as described at 6.6.

Before application, the surface of the wound should be as dry as possible.

See 6.6 for more detailed instructions.

4.3 Contraindications

ARTISS is not indicated to replace skin sutures intended to close surgical wound.
ARTISS alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.
ARTISS must never be applied intravascularly.

Hypersensitivity to the active substances or to any of the excipients (see also section 4.4. Special Warnings).

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.

ARTISS is not indicated for hemostasis 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.

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

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.

As with any protein-containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalized 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 or severe hypersensitivity reactions, administration is to be discontinued, already applied, polymerised product should be removed from the surgical site and 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 HIV, HBV, and HCV, and for the non-enveloped 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 (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemolytic anemia).

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. Similar to comparable products or thrombin solutions, the product may be 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.

4.6 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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalized 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/hemostatics.

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.

Adverse reactions reported from clinical studies as well as from postmarketing surveillance are summarized in the following. Known frequencies of these adverse reactions are based on a controlled clinical study in 138 patients where skin grafts were fixed to excised burn wounds using ARTISS. None of the events were classified as serious. Unknown frequencies are based on spontaneous reports from postmarketing surveillance of Baxter's fibrin sealants.

The ADRs and their frequencies are summarized below:

Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Unknown (cannot be estimated from the available data)

Immune system disorders:

Frequency unknown: anaphylactic responses, hypersensitivity;

Cardiac disorders:

Frequency unknown: bradycardia, tachycardia;

Vascular disorders:

Frequency unknown: hypotension, haematoma;

Respiratory, thoracic and mediastinal disorders:

Frequency unknown : dyspnoea;

Gastrointestinal disorders:

Frequency unknown: nausea;

Skin and subcutaneous tissue disorders:

Common*: pruritus;

Uncommon*: dermal cyst;

Frequency unknown: urticaria;

General disorders and administration site conditions:

Frequency unknown: flushing, impaired healing, oedema, pyrexia;

Injury, poisoning and procedural complication:

Common*: skin graft failure;

Frequency unknown: seroma;

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics, 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 hematoma 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.

* In the controlled clinical study these adverse reactions also occurred at the control site without ARTISS application.

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 anti-fibrinolytics. Aprotinin is present in ARTISS (frozen) 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 (frozen and lyophilized presentations) demonstrated efficacy regarding sealing autologous split skin grafts and mesh grafts.

ARTISS (frozen) was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomised, 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 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 (frozen) and 47/127 patients (37%) treated with staples.

With respect to secondary endpoints, ARTISS 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 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 ($p < 0.0001$).

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/hemostatics are metabolized 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.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store and transport frozen (at ≤ -20°C).

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 controlled room temperature (not exceeding +25°C).Do not refreeze or refrigerate after thawing.

6.5 Nature and contents of container

1 ml, 2 ml, or 5 ml of sealer protein solution and 1, 2 or 5 ml of Thrombin Solution in a single-use double-chamber syringe (polypropylene) with a tip-cap in a bag , and one set device 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 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

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

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

Handling and Preparation

The inner bag and its contents are sterile unless the integrity of the outside package is compromised.

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. (In order to control the specified temperature range, the water temperature should be monitored using a thermometer and the water should be changed as necessary. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum-plastic bags.)

The protective syringe cap should not be removed until thawing is complete and the application tip is ready to be attached. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

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

1. Room Temperature Thawing (not exceeding +25°C):

The product can be thawed at room temperature. Times given in Table 1 are minimum times for thawing at room temperature. The maximum time the product can be kept (in both aluminum-plastic bags) at room temperature is 14 days.

When thawing at room temperature, the product must be additionally warmed to 33°C – 37°C in an incubator just before use. Respective warming times in the incubator are also given in Table 1.

Table 1: Thawing times at Room Temperature (= RT) followed by an additional warming, prior to use, in Incubator at 33°C to a maximum of 37°C

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

Once ARTISS has been warmed up to 33 – 37°C the product may be stored for up to 4 hours.

2. Quick Thawing:

Table 2: Thawing and Warming Times with Sterile Water Bath at 33°C to a maximum of 37°C

Transfer plunger and the inner pouch to the sterile field, remove prefilled syringe from inner pouch and place directly into sterile water bath. Ensure the contents of the prefilled syringe are completely immersed under the water.

Pack Size	Thawing and Warming Times (Product Removed from aluminum-plastic bags)
2 ml	5 minutes
4 ml	5 minutes
10 ml	12 minutes

A third alternative is to thaw the product off the sterile field using a non-sterile water bath.
Maintain the prefilled syringe 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 with prefilled syringe and plunger to the sterile field.

Table 3: Thawing and Warming times off the Sterile Field with Non-Sterile Water Bath at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times (Product in aluminum-plastic bags)
2 ml	30 minutes
4 ml	40 minutes
10 ml	80 minutes

Alternatively, the sealant components may be thawed and warmed in an incubator between 33°C and 37°C. The thawing and warming times in the incubator are indicated in Table 4 below. The times refer to product in the aluminum-plastic bags.

Table 4: Thawing and Warming Times in Incubator at 33°C to a maximum of 37°C

Pack Size	Thawing and Warming Times in Incubator (Product in aluminum-plastic bags)
2 ml	40 minutes
4 ml	85 minutes
10 ml	105 minutes

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

After Quick Thawing (i.e. thawing at a temperature of 33 – 37°C) ARTISS may be stored at 33 – 37°C for a maximum of 4 hours.

To facilitate optimal blending of the two solutions, the two sealant components must be warmed to 33 – 37°C immediately before use. (The temperature of 37°C must, however, not be exceeded!)

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration or any variation in physical appearance. In the event of either being observed, discard the solution.

The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (e.g., due to an interruption of the cold storage chain or by overheating during warming). In this case, ARTISS must not be used.

Unopened pouches, thawed at room temperature, may be stored for up to 14 days at controlled room temperature (not exceeding +25°C). If not used within 14 days after thawing, ARTISS has to be discarded.

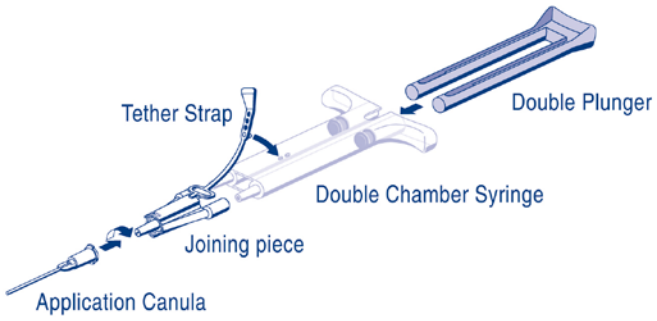
The protective syringe cap should not be removed until use. Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

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

ADMINISTRATION

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 as provided in the accompanying set of devices. The common plunger of the double-chamber syringe ensures that equal volumes are fed through the joining piece before being mixed in the application cannula and ejected.

Operating Instructions



- 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. If the pull strap tears, 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.
- 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.
- Immediately before application expel and discard the first several drops from the application cannula to ensure adequate mixing of the sealer protein and Thrombin Solutions
- 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. Replace the application cannula with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

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

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[to be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed nationally]

10. DATE OF REVISION OF TEXT