1 ARTISS (4IU topical solution)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aprotinin (synthetic), factor XIII, fibrinogen, thrombin and calcium chloride dihydrate.

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. Each solution is presented in a separate preloaded chamber of one double-chamber syringe:
chamber one [1] contains Sealer Protein Solution (with aprotinin), deep frozen (1mL, 2mL or 5mL), chamber two [2] contains Thrombin Solution (with calcium chloride), deep frozen (1mL, 2mL or 5mL), resulting in 2mL, 4mL or 10mL total volume of product ready for use.

Biological origin of active substance
Produced from pooled human plasma.

Composition of the active ingredients of ARTISS

(1) Sealer Protein Solution: 1mL of the solution contains

Active Ingredients	Quantity
As total protein	96 – 125mg
Fibrinogen (Clottable Protein)	72 – 110mg
Factor XIII (human)	1.2 – 10IU
Aprotinin, Synthetic (Fibrinolysis Inhibitor)	2250 – 3750KIU[1]

ARTISS contains Human Factor XIII co-purified with Human Fibrinogen in a range of 1.2 – 10.0IU/mL.

(2) Thrombin Solution: 1mL of the solution contains

Active Ingredients	Quantity
Thrombin (human)	3.2 – 5IU[2]
Calcium Chloride dihydrate (2 H_2O)	36 – 44µmol

For the full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

Topical solution.

The two components of **ARTISS** are colourless to pale yellow, opalescent when frozen and clear to slightly turbid solutions once defrosted.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ARTISS is indicated to adhere:

- autologous skin grafts in burn patients.
- tissue flaps during facial rhytidectomy surgery (face-lift).

ARTISS is not indicated for haemostasis.

1 KIU = Kallidinogenase Inactivator Unit.

2 Thrombin activity is calculated using the current WHO International Standard for thrombin.

4.2 Dose and method of administration

ARTISS should be administered topically. Do not inject.

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

ARTISS should be used by physicians who have been educated on or trained in the use of **ARTISS**.

Application of the product must be individualised to the patient by the treating physician. It is recommended that the initial application cover the entire intended application area.

Repeat application may be necessary, for example, to cover a gap in an **ARTISS** layer after initial application. In such a case, re-application of **ARTISS** should be limited to the area of the gap itself. Application beyond the gap should be avoided as a new layer of **ARTISS** may not adhere firmly to a layer of already polymerized **ARTISS** from the initial application.

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 graft or flap adheres firmly to the underlying tissue.

It is strongly recommended that every time a patient receives a dose of **ARTISS**, the name and batch number of the product are recorded in order to maintain a record of the batches used.

Cannula

The cannulas included with the DUPLOJECT Preparation and Application System (DUO AST Set or PRIMA Set) may be used for small wounds or for edges of a skin graft that did not adhere to the wound bed.

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.

The wound surface should be as dry as possible before application of **ARTISS**. Apply **ARTISS** thinly (2mL/100cm^2) to avoid formation of excessive granulation tissue and interference with wound healing.

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 (Y connector) facing the cannula is clogged, use the spare joining piece provided in the package.

Spray set

For large surface areas, spray application is recommended. The required dose 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
100cm²	2mL
200cm²	4mL
500cm²	10mL

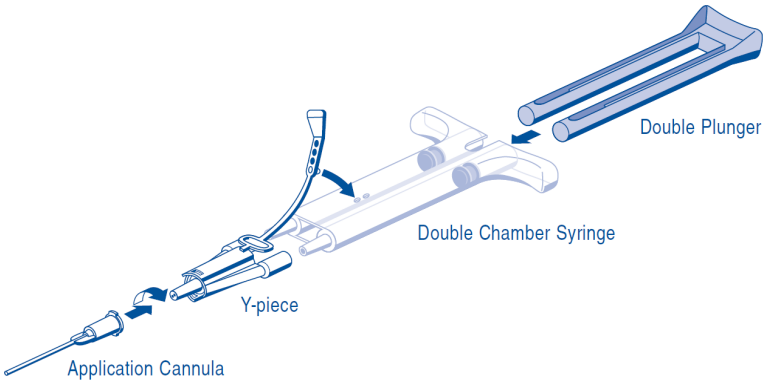
This recommended dose applies to all age groups.

For information on preparation before administration see Section 6.6.

Operating Instructions

Cannula

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.



Device Set Instructions: firmly connect the double chamber syringe nozzles to the Y–piece and secure it by fastening the tether strap to the syringe. Fit an application cannula onto the Y-piece. To avoid clogging, do not expel the air remaining inside the Y-piece or application cannula until application.

Spray set

See package insert of the spray set for instructions on administration of **ARTISS** using the spray set.

Air embolism has occurred with the use of a spray device to administer fibrin sealant (see section 4.8). This appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

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

- Any application of pressurized air or gas is associated with a potential risk of air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening or fatal.
- 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 pressure 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.
- **ARTISS** with the spray set must not be used in enclosed body areas.
- **ARTISS** must be sprayed only onto application sites that are visible.
- **ARTISS** must not be applied intravascularly.
- The user must follow the instructions and precautions in the Easy Spray device user manual, for example regarding the need to limit the gas pressure to a maximum of 2 bars and not be sprayed if the distance is closer than 10cm from the tissue surface.

- To reduce the risk of a potentially life-threatening gas embolism when applying **ARTISS** using a spray device, be sure to use a pressure within the pressure range recommended by the spray device manufacturer. **ARTISS** spray application should only be used if it is possible to accurately judge the spray distance and do not spray closer than recommended by the manufacturer.
- Only use application devices licensed/CE Marked for the administration of **ARTISS**.
- When spraying **ARTISS**, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of air or gas embolism.

See section 6.2.

4.3 Contraindications

Known hypersensitivity to aprotinin or known hypersensitivity to any other component of **ARTISS**, listed in section 6.1.

Injection of **ARTISS** into tissues is contraindicated. Such use has been associated with inadvertent intravascular injection, with thromboembolic complications.

ARTISS should be applied with caution to minimise any risk of intravascular application. **ARTISS** should only be applied topically.

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

4.4 Special warnings and precautions for use

Viral and prion risk

Sealer Protein Solution and Thrombin Solution are made from human plasma. Products made from human plasma may contain infectious agents which can cause disease, such as viruses and theoretically, the agent that causes Creutzfeldt-Jakob Disease (CJD) in humans. 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 inactivation/removal of enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against small 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 red blood cell turnover (e.g., haemolytic anaemia).

All infections thought by a clinician possibly to have been transmitted by **ARTISS** should be reported by the clinician or other healthcare provider to Baxter.

Patients should be instructed to consult their clinician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose, followed about two weeks later by a rash and joint pain).

General

Administration of **ARTISS** may result in allergic reactions in some patients. For patients with a known allergic diathesis, a history of hypersensitivity to medical products or a history of having previously received aprotinin-containing products (including previous use of **ARTISS**) a careful risk-benefit assessment should be carried out prior to administration. The risk of immunisation against

proteins such as aprotinin is increased if repeated exposure occurs within six months. If it is decided to proceed with treatment in such patients, prior administration of antihistamines should be considered.

Manifestations of hypersensitivity reactions to **ARTISS** observed include: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnoea, nausea, urticaria, angioedema, pruritus, erythema, paraesthesia. Fatal anaphylactic reactions, including anaphylactic shock, have also been reported with **ARTISS**. Refer to section 4.8. Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients. Because of the risk of intravascular injection, the product must not be injected into highly vascularised tissue, such as nasal mucosa.

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

Air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening, have occurred with the use of spray devices employing a pressure regulator to administer **ARTISS**. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

To reduce the risk of a potentially life-threatening gas embolism, when applying **ARTISS** using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 1.4 – 1.7 bars (20 – 25psi). Do not spray if the distance is closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10 – 15cm from the surface of the tissue. 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.

As the Sealer Protein and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals (e.g. in disinfectants), any such substances should be removed before application. Refer to section 6.2.

If possible, cover all tissue adjacent to the site of sealing before applying **ARTISS**.

Apply **ARTISS** in a thin layer. Excessive clot thickness may interfere with the product's efficacy and the wound healing process.

Use in elderly

Thirteen subjects aged 65 and older (40 – 71 years of age) have been treated with **ARTISS** in facial rhytidectomy clinical studies. Separate evaluations of these subjects were not performed.

Paediatric use

In the burns setting, efficacy and safety in the paediatric population was not different from the adult population.

Effects on laboratory tests

The effect of this medicine on laboratory tests has not been established.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with **ARTISS**. No known interactions based upon the absence of data from clinical trials, current medical/scientific literature, and post marketing safety reports.

Refer to section 6.2 for more detailed information on interactions with substances other than medicines.

4.6 Fertility, pregnancy and lactation

Fertility

Studies of the effect of **ARTISS** on fertility have not been performed.

Pregnancy (Category B2)

The safety of **ARTISS** for use in human pregnancy has not been established in controlled clinical studies. Animal studies have also not been performed. Physicians should carefully consider the potential risks and benefits for each patient before prescribing **ARTISS**.

Therefore, the product should be administered to pregnant women only if clearly needed. See section 4.4 Viral and Prion Risk for information on Parvovirus B19 infection.

Breast-feeding

The safety of **ARTISS** for use in breastfeeding has not been established in controlled clinical studies. Animal studies have also not been performed. Physicians should carefully consider the potential risks and benefits for each patient before prescribing **ARTISS**. Therefore, the product should be administered to lactating women only if clearly needed.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Adverse reactions from clinical trials

In a phase 3, multi-centred, prospective, evaluator-blinded, randomized study, where **ARTISS** was used to affix split thickness sheet skin grafts to excised burn wounds, a total of 8 non-serious adverse reactions were reported. There were no serious reactions.

The eight non-serious adverse reactions occurred in six patients. Five of these reactions were skin graft failures, 4 were graft detachment/non-adherence, and 1 was graft necrosis. The remaining non-serious adverse reactions were pruritus (2) and dermal cyst (1).

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	Preferred MedDRA Term	Frequency	Frequency ratio
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dermal cyst Pruritus	Uncommon Common	1/138 2/138
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Skin graft failure	Common	5/138
Legend: ADR frequency is based upon the following scale: very common (> 1/10), common (≥ 1/100 - < 1/10), uncommon (≥ 1/1,000 - < 1/100), rare (≥ 1/10,000 - < 1/1,000), very rare (< 1/10,000)			

There were no reports of serious, associated adverse reactions reported above 1% in the facial rhytidectomy clinical studies.

Post-marketing adverse reactions

There are limited post-marketing data available for **ARTISS**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to medicine exposure.

Adverse reactions reported from clinical studies as well as from post-marketing surveillance of Baxter´s other fibrin sealants are summarized in the following. Unknown frequencies are based on spontaneous reports from post-marketing surveillance of Baxter's fibrin sealants.

Immune system disorders

Frequency unknown: hypersensitivity reactions (including anaphylactic reactions, anaphylactic shock, and the following manifestations: angioedema, paraesthesia, bradycardia, tachycardia, flushing, bronchospasm, dyspnoea, wheezing, urticaria, pruritus, and erythema). Anaphylactic reactions and anaphylactic shock have included fatal outcomes.

Cardiac disorders

Frequency unknown: bradycardia, tachycardia.

Vascular disorders

Frequency unknown: hypotension, haematoma and air embolism*.

**Air embolism associated with misapplication of fibrin sealant using a spray device*

There are reports of life threatening/fatal air or gas embolism associated with the use of fibrin sealants when applied using a spray device at higher than the recommended pressure and closer than the recommended distance in an attempt to stop active bleeding.

Respiratory, thoracic and mediastinal disorders

Frequency unknown: dyspnoea.

Gastrointestinal disorders

Frequency unknown: nausea.

Skin and subcutaneous tissue disorders

Common: pruritis.
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.

Class reactions

Manifestations of hypersensitivity or allergic reactions associated with the class of fibrin sealant/haemostatic products include: application site irritation, chest discomfort, chills, headache, lethargy, restlessness and vomiting. There have been no reports of these reactions related to the specific use of **ARTISS**.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 the individual components should be applied.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

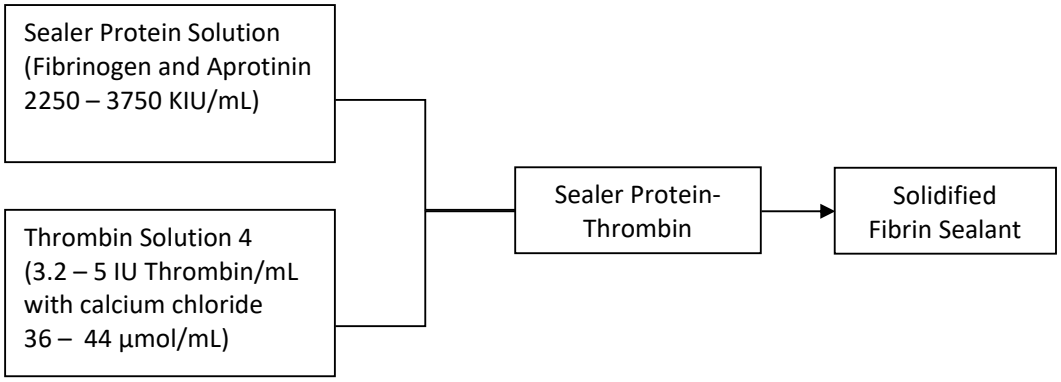
Pharmacotherapeutic groups:	BLOOD AND BLOOD FORMING ORGANS, ANTIHEMORRHAGICS, VITAMIN K AND OTHER HEMOSTATICS, Local hemostatics	VARIOUS, ALL OTHER THERAPEUTIC PRODUCTS, ALL OTHER THERAPEUTIC PRODUCTS, Tissue adhesives
ATC codes:	B02BC	V03AK

Mechanism of action

ARTISS contains two components, Sealer Protein Solution and Thrombin Solution. The Sealer Protein Solution contains fibrinogen as the main active ingredient, the active ingredient of the Thrombin Solution is human thrombin. These mimic the final step of the coagulation cascade.

The thrombin converts fibrinogen to fibrin which then polymerizes and is crosslinked by factor XIIIa to form a clot. Due to the low concentration of thrombin in **ARTISS**, clotting takes about a minute. Clotting causes tissues to adhere and provides a matrix for the in-growth of fibroblasts and capillaries which helps vascularisation and wound healing. The matrix is eventually broken down and absorbed in a process called fibrinolysis. Aprotinin in **ARTISS** delays fibrinolysis.

The following diagram illustrates the conversion of fibrinogen to fibrin, and polymerization.



ARTISS containing 4IU thrombin has demonstrated adhesion of autologous split skin grafts to surgically prepared wound beds in a pig model.

Clinical trials

Burn (grafts)

ARTISS (frozen) was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomised, controlled, multicentre clinical study, conducted in 138 burn subjects. In each subject, 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).

The intent-to-treat (ITT) population reported in the study included 127 of the treated subjects. The 11 treated subjects not included in the study ITT population were excluded for one of the following reasons: no primary endpoint assessment at both test sites (one subject); lost to follow-up prior to Day 28; or photographs not taken on both test sites on Day 28. The median age of subjects was 31 years, range 1 – 62 years, 14% were ≤ 6 years of age and 15% 7 – 18 years of age, 66% of the subjects were male. Similar areas were treated at the two sites: 1.7 ± 0.8% body surface area at **ARTISS** sites and 1.7 ± 0.7% body surface area at stapled sites. Burn thickness was full in 77% of subjects and partial in 23%. The most commonly grafted sites were the lower arms and lower legs.

ARTISS 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 was evaluated by a blinded evaluator panel from Day 28 photographs.

Results for wound closure on Day 28 are given in the following table:

Test sites with complete wound closure on Day 28				
	ARTISS	Staples (control)	Difference [95% CI]	Difference [97.5% CI][1]
Modified Intent to Treat Analysis	55 of 127 (43.3%)	47 of 127 (37.0%)	6.3% [-2.9%, 15.5%]	6.3% [-2.9%, -]
Per Protocol Analysis	48 of 106 (45.3%)	42 of 106 (39.6%)	5.7%	5.7% [-4.1%, -]
[1] The non-inferiority criterion was a lower limit of the 97.5% confidence interval of the difference between treatments > -10%.				

There was support from the secondary endpoints which were evaluated by the investigator (see following table).

Summary of Secondary Efficacy Endpoints – Categorical Variables/Intent-to-Treat			
	ARTISS	Staples	Difference [95% CI]
	[n of N (%)]	[n of N (%)]	
Presence of Haematoma/ seroma on Day 1	41 of 138 (29.7%)	86 of 138 (62.3%)	-32.6% [-41.4%, -23.8%]
100% Engraftment on Day 5	86 of 138 (62.3%)	76 of 138 (55.1%)	7.2% [-0.2%, 14.7%]
Complete Wound Closure on Day 14	63 of 129 (48.8%)	55 of 129 (42.6%)	6.2% [-2.6%, 15.0%]

Facial rhytidectomy (flaps)

ARTISS was investigated for adherence of skin flaps in facial rhytidectomy surgeries during two prospective, randomized, controlled, multicenter clinical studies. Both studies had a split-face design in which one side of the face was treated with **ARTISS** and the other side received standard of care (SoC); therefore each subject participated in both arms (**ARTISS** and SoC). In the Phase 2 study,

ecchymosis evaluation was performed by an independent panel of 5 blinded reviewers. 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. Pressure dressings were not permitted.

The combined study population consisted of 120 subjects of which 113 (94.2%) were female and 7 (5.8%) were male. The mean ± SD age was 54.7 ± 7.2 years (range: 40 – 71 years). The mean ± SD weight was 66.5 ± 11.9kg. By race, 116 (96.7%) were white, 2 (1.7%) were black, 1 (0.8%) was Asian, and 1 (0.8%) was of multi race. Ethnicity was Hispanic or Latino in 5 (4.2%) subjects. Overall, the demographic and baseline characteristics were similar for both studies, allowing comparison of appropriate efficacy outcomes.

The endpoints analysed for the two studies are:
- Drainage volumes at 24h post operatively, for each side of the face (see the following table)
- Occurrence of haematoma and seroma (see table below).

Drainage Volume Comparison at 24h 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, 45 subjects	11.5 ± 13.7	26.8 ± 24.0	< 0.001
Phase 3, 75 subjects	7.7 ± 7.4	20.0 ± 11.3	< 0.001

An integrated analysis of the occurrence of haematoma/seroma in all 120 subjects across two studies was performed. A comparison was made of the proportion of subjects experiencing a haematoma/seroma exclusively on the **ARTISS**-treated side 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 Haematoma/Seroma			
ARTISS n (%)	SoC, n (%)	Both Sides of Face, n (%)	Total, n (%)
2 (1.7%)	14 (11.7%)	3 (2.5%)	19 (15.8%)

Chemical structures

Fibrinogen

The major component of the clottable protein (human origin) is fibrinogen. The fibrinogen molecule is a dimer composed of two symmetrical subunits linked by -S-S- bonds. It could be written in a simple formula as $(A\alpha, B\beta, \gamma)_2$.
Molecular weight (MW) : 340 000. The $A\alpha$-chain contains 610 amino acids (MW about 68 000), the $B\beta$-chain 461 amino acids (MW about 57 000), and the γ-chain 411 amino acids (MW about 47 000). Thus, the entire human fibrinogen contains 2964 amino acids.
CAS No.: 9001-32-5

Thrombin

Thrombin (human origin) is a glycosylated protein, consisting of two polypeptide subunits A and B, covalently linked by one -S-S- bond.
Molecular weight (MW): 33 800. The human thrombin subunit A chain is made of 36 amino acids, whilst the B chain contains 259 amino acids.
CAS No.: 9002-04-4

Factor XIII

Factor XIII (human origin), also called blood-coagulation factor XIII, is a tetramer composed of two a-chains and two b-chains which are non-covalently associated.
Molecular weight (MW): about 190 000 (each of a molecular weight of about 80 000).
CAS No.: 9013-56-3

Aprotinin

Aprotinin (synthetic origin) inhibitor, a polypeptide consisting of one chain of 58 amino acids stabilized by -S-S- bonds.
Molecular weight (MW): 6511.5
CAS No.: 9087-70-1

Calcium chloride dihydrate

Molecular formula: $CaCl_2.2H_2O$
Molecular weight: 147.01
CAS number: 10035-04-8
Appearance: a white crystalline powder
Solubility: hydroscopic, freely soluble in water.

5.2 Pharmacokinetic properties

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

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

5.3 Preclinical safety data

Genotoxicity

Studies of genotoxic potential of **ARTISS** have not been performed.

Carcinogenicity

Animal studies to evaluate the carcinogenic potential of **ARTISS** have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Composition of the excipients of ARTISS

	Sealer Protein Solution	Thrombin Solution
Excipients	1mL of the solution contains: Human albumin (10 – 20mg) Histidine (10 – 25mg) Sodium citrate (4.8 – 9.7mg) Polysorbate 80 (0.6 – 1.9mg) Nicotinamide (3 – 9mg) Water for injection q.s. to 1mL.	1mL of the solution contains: Human albumin (45 – 55mg) Sodium chloride (3.5 – 5.5mg) Water for injection q.s to 1mL.

6.2 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 and dried before application of **ARTISS**.

Oxidised 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.

6.3 Shelf life

24 months: Deep frozen **ARTISS** has a shelf life of two (2) years when stored at or below −18°C. The expiry date is stated on the final container and the package.

14 days: Unopened pouches, thawed at room temperature, may be stored for up to 14 days at or below controlled room temperature (not exceeding +25°C). If not used within 14 days after thawing, **ARTISS** must be discarded. After thawing, the solutions must not be refrigerated or refrozen.

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

6.4 Special precautions for storage

Store in a freezer at −18°C or colder. The cold storage chain must not be interrupted until use. Keep container in the outer carton to protect from light. After quick thawing (i.e. thawing at a temperature of 33 – 37°C) unopened **ARTISS** may be stored at 33 – 37°C for a maximum of 4 hours. Once thawed, do not refreeze or refrigerate.

Keep out of reach and sight of children. For single use only. Do not re-sterilise.

6.5 Nature and contents of container

Nature of containers

Both Sealer Protein Solution and Thrombin Solution are contained in two separate chambers of a single use double chamber syringe made of polypropylene.

Contents

Each pack of **ARTISS** contains:

- One single use double chamber syringe, each chamber containing:
  - Chamber number [1]: Sealer Protein Solution (with aprotinin) deep frozen
  - Chamber number [2]: Thrombin Solution (with calcium chloride) deep frozen
- One set of devices (see below).

Set of devices

Each pack of **ARTISS** contains a double-sterile set of devices (AST or PRIMA) consisting of one syringe double-plunger, two Y-pieces and four application cannulas. These devices are used for the simultaneous application of the fibrin sealant components. For details on application and complications associated therewith see section 4.2 (Operating Instructions).

The set of devices is sterile and non-pyrogenic in unopened and undamaged package. Sterilised by exposure to ethylene oxide.

ARTISS is available in the following pack sizes
ARTISS, 2.0mL (containing 1.0mL of Sealer Protein Solution and 1.0mL of Thrombin Solution)

ARTISS, 4.0mL (containing 2.0mL of Sealer Protein Solution and 2.0mL of Thrombin Solution)

ARTISS, 10.0mL (containing 5.0mL of Sealer Protein Solution and 5.0mL of Thrombin Solution).

6.6 Special precautions for disposal and other handling

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

The **ARTISS** solutions contain no antimicrobial agent. **ARTISS** is intended for single use in one patient only and unused solution in the syringe should be discarded.

Method of preparation of ARTISS preloaded syringe (Frozen)

- 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** must be discarded.
- To facilitate optimal blending of the two solutions, the two sealant components must be warmed to 33 - 37°C immediately before use.
- **ARTISS** must not be exposed to temperatures above 37°C and must not be microwaved.
- 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 prevent **ARTISS** from adhering, wet gloves and instruments with sodium chloride solution before contact.
- Do not use **ARTISS** unless it is completely thawed and warmed (liquid consistency). The protective syringe cap should not be removed until storage, thawing and warming is complete and application tip is ready to be attached.

For quick thawing of the preloaded syringe use one of the three following options

Option 1 – Thawing on the sterile field

33°C to 37°C sterile water bath - transfer devices set and the inner pouch to the sterile field, remove devices set with preloaded syringes from inner pouch and place directly into sterile water bath. Ensure the contents of the syringe are 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)	
	AST	PRIMA
2mL	5 minutes	5 minutes
4mL	5 minutes	5 minutes
10mL	12 minutes	10 minutes

Option 2 – Thawing off the sterile field using water bath

33°C to 37°C non-sterile water bath in two pouches - maintain the devices 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 preloaded syringe 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)	
	AST	PRIMA
2mL	30 minutes	15 minutes
4mL	40 minutes	20 minutes
10mL	80 minutes	35 minutes

Option 3 – Thawing off the sterile field using incubator

Incubate (33°C to 37°C) in pouches – maintain the devices set in both pouches and place into an incubator for appropriate time. Remove from incubator after thawing and transfer inner pouch and preloaded syringe 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)	
	AST	PRIMA
2mL	40 minutes	40 minutes
4mL	85 minutes	50 minutes
10mL	105 minutes	90 minutes

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
15 March 2012.

10 DATE OF REVISION OF THE TEXT

13 July 2021.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Calcium chloride dihydrate in full Reference to excipients removed from table and statement moved to end of section.
4.2	Inclusion of PRIMA set as one of the application systems.
5.1	Heading corrected to 'Mechanism of action'. Flow diagram values corrected. Chemical structure information updated and inclusion of CAS numbers.
6.5	Inclusion of PRIMA set as one of the application systems Pack sizes moved to end of section.
6.6	Method of preparation updated to include PRIMA thawing/warming times.

Based on CCDS 2017 2014 1001.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.