



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Fibrin sealant

Proprietary Product Name: Artiss

Sponsor: Baxter Healthcare Pty Ltd

**October 2010**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Contents

<b>I.</b>	<b><i>Introduction to Product Submission</i></b> .....	<b>4</b>
	Submission Details.....	4
	Product Background.....	4
	Regulatory Status.....	5
	Product Information.....	6
<b>II.</b>	<b><i>Quality Findings</i></b> .....	<b>6</b>
	Introduction.....	6
	Drug Substance (active ingredient).....	6
	Drug Product.....	7
	Quality Summary and Conclusions.....	10
<b>III.</b>	<b><i>Nonclinical Findings</i></b> .....	<b>10</b>
	Introduction.....	10
	Pharmacology.....	11
	Pharmacokinetics.....	13
	Toxicology.....	13
	Nonclinical Summary and Conclusions.....	15
<b>IV.</b>	<b><i>Clinical Findings</i></b> .....	<b>17</b>
	Introduction.....	17
	Pharmacokinetics and Pharmacodynamics.....	18
	Efficacy.....	18
	Safety.....	30
	Clinical Summary and Conclusions.....	32
<b>V.</b>	<b><i>Pharmacovigilance Findings</i></b> .....	<b>33</b>
	Risk Management Plan.....	33
<b>VI.</b>	<b><i>Overall Conclusion and Risk/Benefit Assessment</i></b> .....	<b>34</b>
	Quality.....	34
	Nonclinical.....	34
	Clinical.....	34
	Risk Management Plan.....	35
	Risk-Benefit Analysis.....	35
	Outcome.....	36
	<b><i>Attachment 1. Product Information</i></b> .....	<b>36</b>

## I. Introduction to Product Submission

### Submission Details

<i>Type of Submission</i>	New Biological Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	3 August 2010
<i>Active ingredient(s):</i>	Fibrin sealant
<i>Product Name(s):</i>	Artiss
<i>Sponsor's Name and Address:</i>	Baxter Healthcare Pty Ltd 1 Baxter Drive Old Toongabbie NSW 2146
<i>Dose form(s):</i>	Two deep frozen solutions in pre-filled syringes
<i>Strength(s):</i>	1 mL, 2 mL and 5 mL of each solution
<i>Container(s):</i>	Both Sealer Protein Solution and Thrombin Solution are contained in two separate chambers of a single use double chamber syringe made of polypropylene.
<i>Pack size(s):</i>	2 mL, 4 mL and 10 mL
<i>Approved Therapeutic use:</i>	Artiss is indicated to adhere autologous skin grafts in burns patients. Artiss is not indicated for haemostasis.
<i>Route(s) of administration:</i>	Topical
<i>Dosage:</i>	Individualised – see Product Information
<i>ARTG Number:</i>	163515

### Product Background

Artiss Fibrin Sealant VH S/D 4IU (FS VH S/D 4 IU) is a human plasma-derived biological product for local administration indicated for adhesion/sealing of tissues and as an adjunct to haemostasis on subcutaneous tissue surfaces. Artiss is a haemostatic agent consisting of two deep frozen solutions, Sealer Protein Solution and Thrombin Solution, preloaded in a double-chamber syringe. The Sealer Protein Solution contains human fibrinogen, human factor XIII and synthetic aprotinin. The Thrombin Solution contains human thrombin (4 IU/mL) and calcium chloride. The solutions are thawed and warmed to 37°C, then mixed during application. The basic principle of fibrin sealing is to imitate the final steps of blood coagulation with concentrated solutions of fibrinogen and thrombin. Upon mixing of these two biologic components, soluble fibrinogen is transformed into fibrin, forming a rubber-like mass that adheres to the wound surface and achieves adhesion or sealing of tissues and haemostasis. During the course of wound healing, the solidified fibrin sealant is slowly lysed and completely resorbed while new tissue is formed. A fibrinolysis inhibitor, aprotinin, precludes premature fibrinolysis, which might cause detachment of sealed or glued tissue parts or re-bleeding.

Artiss is manufactured using both vapour heat (VH) treatment and solvent/detergent (S/D) treatment as two independent viral inactivation steps. It has a factor XIII content of < 10 IU/mL.

The proposed product is essentially similar to Tisseel VH S/D (frozen) fibrin sealant syringe (AUST R 147141), which has approved indications as an adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical, and as a sealant as an adjunct for closure of colostomies. Tisseel contains a higher concentration of thrombin in the Thrombin Solution (500 IU/mL) and is registered as an adjunct to haemostasis in surgical procedures and an adjunct in closure of colostomies and autologous chondrocyte implantation. The aprotinin in Tisseel is bovine-derived. An application to replace bovine with synthetic aprotinin is under evaluation. The high concentration of thrombin enables fast haemostasis and sealing. Artiss has a longer clotting time than Tisseel, which is an advantage in the proposed indications where additional manipulation may be required after applying the sealant.

Major safety issues with these products are hypersensitivity reactions, thromboembolism and infection from blood-borne viruses and transmissible spongiform encephalopathy (TSE).

There is a TGA-adopted European Union (EU) guideline on the clinical investigation of these products.<sup>1</sup>

The indication proposed by the sponsor is as follows:

*Artiss is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery. 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.*

*In addition, Artiss is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces, for example in the procedures mentioned above.*

### **Regulatory Status**

A similar application for Fibrin Sealant VH S/D with 4 IU Thrombin containing synthetic aprotinin was approved in the US in 2008. This product is identical to the Artiss product submitted in this application and the dataset submitted in Australia is similar to that submitted in the US. The US approved indication is as follows:

*Artiss is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and paediatric populations. Artiss is not indicated for haemostasis.*

An application for the synthetic aprotinin preparation was approved in Canada in May 2009 for the following “package” indication:

*Tisseel (Fibrin Sealant (Human), Vapor Heated, Solvent Detergent Treated) is used in addition to standard measures, to achieve haemostasis, to seal or glue tissue, and to support wound healing.*

*Indications include: abdominal surgery, cardiovascular surgery, orthopedic surgery, thoracic surgery, urology, fixation of autologous skin grafts and skin flaps and adjunct to hemostasis on subcutaneous tissue surfaces to treat burns in adult and pediatric patients.”*

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<sup>1</sup> EMEA, Committee for Medicinal Products for Human Use (CHMP), 29 July 2004. Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products (CPMP/BPWG/1089/00): <http://www.emea.europa.eu/pdfs/human/bpwg/108900en.pdf>.

A similar product containing bovine rather than synthetic aprotinin is approved in the EU with the indication:

*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 and staples. In addition, Artiss is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces.*

## **Product Information**

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## **II. Quality Findings**

### **Introduction**

Artiss and Tisseel VH S/D are plasma-derived fibrin sealants containing the following two components:

Component 1 – Sealer Protein Solution: the active ingredients are aprotinin, factor XIII and fibrinogen.

Component 2 – Thrombin Solution: the active ingredients are thrombin and calcium chloride.

The key differences between Tisseel VH S/D and Artiss are:

Strength of the Thrombin solution: 500 IU/mL for Tisseel VH/SD and 4 IU/mL in Artiss

Proposed indications

The Sealer Protein Solution, container and device set for Artiss are the same as that of Tisseel VH S/D. Therefore, the current application only concerns a change to the manufacture of the Thrombin Solution. Hence, the focus of this summary and the associated quality evaluation reports is the Thrombin Solution.

Tisseel VH/SD was registered in Australia on 13 March 2009. Tisseel VH S/D evolved from Tisseel Duo 500, which was registered in Australia on 28 January 2003. A submission to vary the registration of Tisseel VH S/D is currently under evaluation. The changes proposed in that submission only concern the Sealer Protein Solution, namely the replacement of bovine aprotinin with synthetic aprotinin. The quality evaluation of that Tisseel VH S/D submission has been completed, and there are no outstanding issues relevant to the registration of Artiss.

The formulation of Artiss proposed for Australia contains synthetic aprotinin. The quality data provided for the Sealer Protein Solution (including the bulk drug substance and synthetic aprotinin) in Artiss is the same as that provided in Tisseel VH S/D submission.

Throughout the evaluation reports and the current report, the drug substances are referred to as the Thrombin Bulk and Sealer Protein Bulk, and the drug products are referred to as the Thrombin Solution and Sealer Protein Solution.

### **Drug Substance (active ingredient)**

The manufacture of the drug substances in the Sealer Protein Solution (Sealer Protein Bulk and Synthetic Aprotinin Concentrate) were evaluated as part of previous submissions.

The manufacture of the drug substances in the Thrombin Solution (Thrombin Bulk and calcium chloride dihydrate) were also evaluated previously since the manufacturing process for the Thrombin Bulk in Artiss is the same as that used for Tisseel VH S/D. Briefly, the manufacturing process of the Thrombin Bulk includes the following steps:

Separation of cryoprecipitate

Protein purification including column chromatography and ultrafiltration/diafiltration

Vapour heat treatment

Solvent/Detergent treatment

The Thrombin Bulk is a concentrated solution, which may be stored for up to 12 months at  $\leq -20^{\circ}\text{C}$  or up to 7 days at  $2^{\circ}\text{C} - 8^{\circ}\text{C}$ .

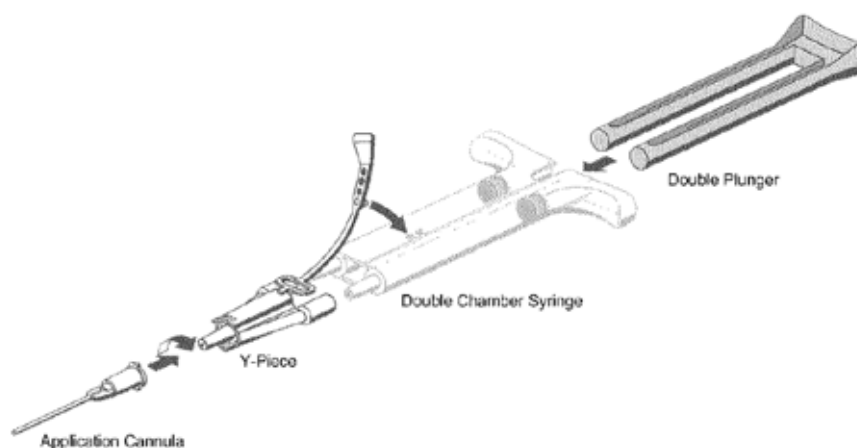
Since the manufacture of the Thrombin Bulk, Sealer Protein Bulk and Sealer Protein Solution is the same for both Tisseel VH S/D and Artiss, the process validation performed previously for Tisseel VH S/D is applicable to the bulks and Sealer Protein Solution in Artiss.

Artiss is covered by the Baxter Bioscience Plasma Master File. The 2008 annual update containing 2007 data was received in January 2009, and approved by the TGA in April 2009.

## Drug Product

### Presentation and formulation

Both components are supplied deep-frozen and are ready to use upon thawing. The two components are combined immediately before the product is applied to the patient using a pre-filled double-chamber syringe application device (Figure 1).



**Figure 1: Double-chamber syringe application device (Duo Set)**

Artiss VH/SD is to be made available in the following pack sizes:

2 mL (1 mL sealer protein solution + 1 mL thrombin solution)

4 mL (2 mL sealer protein solution + 2 mL thrombin solution)

10 mL (5 mL sealer protein solution + 5 mL thrombin solution)

Each Artiss VH/SD fibrin sealant syringe is packed together with one set of sterile accessory devices, the Duo Set (Figure 1), which consists of the following components:

Joining pieces (2 pieces, with tether strap)

Application needles (4 pieces, blunt)

Double syringe plunger (1 piece)

The syringe plunger and tip cap for Artiss is light blue to distinguish it from Tisseel VH S/D, which contains red components. The presentation of the product is otherwise unchanged.

The formulation of the Sealer Protein Solution and the Thrombin Solution is provided in Table 1.

Table 1: Formulation of the drug product

Component	Quantity	Function
<b>SEALER PROTEIN SOLUTION (Component 1)</b>		
<i>Active Ingredients:</i>		
<b>Fibrinogen</b>	<b>72 – 110 mg/mL<sup>a</sup></b>	<b>Clot forming agent</b>
<b>Aprotinin</b>	<b>2250 – 3750 KIU/mL<sup>b</sup></b>	<b>Fibrinolysis inhibitor</b>
<b>Factor XIII</b>	<b>1.2 – 10.0 IU/mL</b>	<b>Clot stabilising agent</b>
<i>Excipient Ingredients:</i>		
<b>Human albumin</b>	<b>10 – 20 mg/mL</b>	<b>To adjust total protein content</b>
<b>L-Histidine</b>	<b>10 – 25 mg/mL</b>	<b>Stabilising agent</b>
<b>Nicotinamide</b>	<b>3 – 9 mg/mL</b>	<b>Viscosity reducing agent</b>
<b>Polysorbate 80</b>	<b>0.6 – 1.9 mg/mL<sup>c</sup></b>	<b>Solubilising agent</b>
<b>Sodium citrate dihydrate</b>	<b>4.8 – 9.7 mg/mL</b>	<b>Stabilising agent</b>
<b>Water for injections</b>	<b>qs</b>	<b>Solvent</b>
<b>THROMBIN SOLUTION (Component 2)</b>		
<i>Active Ingredients:</i>		
<b>Thrombin</b>	<b>3.2 – 5.0 IU/mL</b>	<b>Coagulation factor</b>
<b>Calcium chloride</b>	<b>36 – 44 mmol/mL</b>	<b>Clotting activator</b>
<i>Excipient Ingredients:</i>		
<b>Sodium chloride</b>	<b>3.5 – 5.5 mg/mL</b>	<b>To achieve isotonicity</b>
<b>Protein</b>	<b>45 – 55 mg/mL</b> <b>(Human albumin: <math>\geq</math> 35 mg/mL)</b>	<b>Stabilising agent</b>
<b>Water for Injections</b>	<b>qs</b>	<b>Solvent</b>

<sup>a</sup> Is contained in a total protein of 96 – 125 mg/mL

<sup>b</sup> 1800 Kallidinogenase Inactivator Units (KIU) correspond to 1 European Pharmacopoeia unit (EPU)

<sup>c</sup> Tested at the drug substance level

## Manufacture

The manufacture of the Sealer Protein Solution was evaluated previously.

The manufacturing process of the Thrombin Solution involves the following steps:

- Formulation
- Sterilising filtration
- Sterile filling
- Labelling, packaging and freezing
- Quality control

During the formulation of the drug product, the Thrombin Bulk is diluted to the target concentration of 4.2 IU/mL using Water for Injections. The different target concentration in the formulation step accounts for the different potencies in Artiss and Tisseel VH S/D. The processes are otherwise identical.

The relevant pharmacopoeial monograph for this product is *Fibrin Sealant Kit* (European Pharmacopoeia (Ph. Eur.) monograph 0903. In the monograph the drug products are referred to as *Component 1 (Fibrinogen Concentrate)* and *Component 2 (Thrombin Preparation)*.

The proposed release specifications were evaluated and found acceptable. The analytical procedures for determining thrombin activity and other chemical and microbiological properties relevant to clinical use of the Thrombin Solution are in accordance with the Ph. Eur. The method for the determination of thrombin activity has been modified from that used for Tisseel VH S/D, and is validated for the 4 IU strength Artiss.

Manufacturing process validation data for the 4 IU Thrombin Solution in Artiss was reviewed and considered satisfactory.

## Sterility

Sterility aspects of the product have been reviewed. There were no outstanding issues relating to sterility.



## Container safety

The following material components were assessed:

- Polyethylene bag for storage of drug substance
- Double-chamber syringe (syringe barrel, plunger stopper, tip cap)
- Duo-Set (joining pieces, application cannula, double-syringe plunger)

There were no outstanding issues with regards to container safety.

## Endotoxin/pyrogen safety

The relevant monograph for Artiss does not indicate a bacterial endotoxin test. A test for pyrogens is included in the release specification for the Thrombin Solution. This is the same test that is applied to Tisseel VH S/D, which was previously assessed and determined to be acceptable.

## Viral/Prion safety

The viral and prion safety aspects of the active ingredient and relevant excipients (human albumin and heparin sodium (porcine)) have been reviewed. There were no objections on viral or prion safety grounds to the registration of Artiss.

## Stability

The proposed shelf life of the Thrombin Solution is:

- 24 months when stored at  $\leq -20^{\circ}\text{C}$
- 7 days after thawing (at  $25^{\circ}\text{C}$ , after removal from the freezer) when stored below  $25^{\circ}\text{C}$
- 4 hours after thawing (at  $33-37^{\circ}\text{C}$ , after removal from the original pouches) when stored at  $33-37^{\circ}\text{C}$

Long-term stability data have been generated to characterise the stability profile of the product. The studies have been completed. No trends were apparent upon inspection of the raw data, which demonstrates that the product is relatively stable over the proposed shelf-life.

The acceptance criteria for thrombin activity are tighter for the release than for the shelf-life specifications. This permitted the results for thrombin activity to exceed the release limit at several time points throughout the stability study. The precision and accuracy of the method for testing thrombin activity has been improved since completion of the stability studies but it is a matter of speculation as to whether the results would have remained within the tighter specification if the product was tested using the new method.

The issue of increased thrombin activity was considered to be low risk compared with the converse (low thrombin activity), and therefore a higher upper specification limit for the stability studies was considered acceptable, provided that the tighter specification limit applies at time of release. Therefore, the results were considered to support the proposed shelf-life.

The precision and accuracy of the method for testing thrombin activity has been improved since completion of the stability studies but it is a matter of speculation as to whether the results would have remained within specification if the product was tested using the new method.

Instructions for thawing and/or storage of the product are provided in the PI, CMI and labels. As with Tisseel VH S/D, there are two options for thawing and subsequent storage of product. The stability of the thawed product was evaluated at the end of the shelf life. Product was either thawed at room temperature and subsequently stored at room temperature or thawed at  $37^{\circ}\text{C}$  (after removal from the original pouches) and subsequently stored at  $37^{\circ}\text{C}$ .

The studies have been completed and the results support the proposed shelf-life for the thawed product.

The shelf-life of the Sealer Protein Solution was assessed as part of Tisseel VH S/D submission. Taking into account the shelf life of the Sealer Protein Solution and the data presented in the current submission, the recommended shelf-life for Artiss is:

24 months when stored below -20°C (Deep freeze)

7 days after thawing (at 25°C, after removal from the freezer) when stored below 25°C

4 hours after thawing (at 33-37°C, after removal from the original pouches) when stored at 33-37°C

### **Quality Summary and Conclusions**

There were no objections to the registration of Artiss fibrin sealant VH S/D 4 IU (frozen) on quality grounds.

It was recommended that, as with all new biological entities, it be a condition of registration that the first five batches of Artiss fibrin sealant VH S/D 4 IU (frozen) imported into Australia are not released for sale until: (1) samples of each batch have been tested and approved by the TGA's Office of Laboratories and Scientific Services (OLSS), and (2) the manufacturer's release data have been evaluated and approved by OLSS. These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The sponsor may also be required to provide evidence of satisfactory shipping conditions to Australia for every batch imported. These conditions should remain in place until the sponsor is notified officially in writing of any change.

Five double-chambered syringes of each batch should be provided for testing by the Therapeutic Goods Administration Laboratories together with any necessary standards, impurities and active pharmaceutical ingredients (together with their Certificates of Analysis) for method development and validation.

## **III. Nonclinical Findings**

### **Introduction**

Currently there are two fibrin sealant products registered in Australia (Tisseel Duo 500 and Tisseel VH S/D). Both of them are manufactured by Baxter Healthcare and contain bovine aprotinin and a high concentration (500 IU/mL) of thrombin for instant sealing (haemostasis).

Artiss (deep frozen) is another generation of fibrin sealant manufactured by the same company. This product has the same formulation as Tisseel VH S/D, except for synthetic aprotinin in the Sealer Protein Solution and a low concentration (4 IU/mL) of thrombin in the Thrombin Solution for Artiss. The proposed indications for Artiss are adhesion of subcutaneous tissues in plastic, reconstructive and burn surgery and as an adjunct to haemostasis on subcutaneous tissue surfaces to reflect slow polymerisation, different from the indications of Tisseel.

Recently, the sponsor has applied to change the source of aprotinin from bovine to synthetic for Tisseel VH S/D and the nonclinical aspect of this application is under evaluation. In relation to the reduction (500 to 4 IU/mL) of thrombin concentration in fibrin sealant, there may be some changes in pharmacodynamics, but it is unlikely to have additional safety concerns, compared to those of the registered sealants. Therefore, the evaluation in this report mainly focuses on the pharmacodynamics of the proposed product in relation to the indications proposed and the pharmacodynamic, pharmacokinetic and toxicological comparability between the synthetic and bovine aprotinin.

Among the data provided, there were only four new pharmacodynamic studies included. Other nonclinical studies included in this submission have also been submitted for Tisseel VH S/D containing 500 IU/mL thrombin and bovine aprotinin and for Tisseel VH S/D to change aprotinin source from bovine to synthetic. All studies provided were conducted in compliance with Good Laboratory Practice (GLP).

## Pharmacology

### Primary pharmacodynamics

#### *Inhibitory activities to serine proteases*

Aprotinin is a protease inhibitor. It inhibits several serine proteases including trypsin, chymotrypsin, plasmin and kallikrein, and at very high concentrations, it also has inhibitory activity to thrombin<sup>2</sup>.

No *in vitro* pharmacodynamic studies comparing the activities of synthetic and bovine aprotinin were provided, but the trypsin inhibiting activity of the synthetic aprotinin was determined and evaluated. There were no data on the inhibitory activity of the synthetic aprotinin to other proteases such as plasmin, kallikrein and thrombin. This is considered a deficiency of the nonclinical data package.

#### *Adhesion of subcutaneous tissues*

For tissue gluing with fibrin sealant, all studies provided were conducted using one pig model for adhesion of autologous split skin grafts. Fibrin sealants were applied using the Tissomat (Baxter) spray system to cover large wound areas with a thin fibrin layer.

#### *Effect of thrombin concentration*

Slow polymerisation by a low concentration of thrombin contained in fibrin sealant may be advantageous for adhesion of tissues, in which time for additional tissue manipulation is needed after applying the sealant. In a comparison study for tissue gluing, the effects of Tisseel VH (deep frozen) containing bovine aprotinin and 4 IU/mL thrombin (0.05 or 0.15 mL/cm<sup>2</sup>) were comparable to or slightly better than suture for adhering autologous split skin grafts to surgically prepared wound beds in piglets (about 3 months old). The assessment was based on seroma (0% of the total wound in both groups by Day 7 post-operation) or haematoma (0-4% by fibrin sealant versus 11% by suture on Day 7) formation, take rate (99-100% versus 88% on Day 14) and total wound area healed (100% versus 93% on Day 21). In addition, the fibrin sealant was significantly easier (75-100% versus 0% for the best application) to apply and shorter in grafting time (2-4 minutes versus 13 minutes) than suture. The foreign body reaction and inflammation (degree and/or occurrence) at grafted sites were lower in the fibrin sealant groups, compared to those in the suture group.

#### *Effect of dose*

In the same study, there were no significant differences in outcomes at the grafted area (seroma or haematoma formation, take rate and wound area healed) between the doses (0.05 and 0.15 mL fibrin sealant/m<sup>2</sup>) tested. However, the low dose was easier for application (100% versus 75% for the best application), shorter (2.4 minutes versus 3.6 minutes) in grafting time and had less foreign body reaction than the high dose. Thus the low dose is preferable for application. This effect was confirmed by another group in a similar study<sup>3</sup>.

<sup>2</sup> Levy JH & Synniewski E: Aprotinin: a pharmacologic overview. *Orthopedics* 2004; 27: s653-658.

<sup>3</sup> Mittermayr R, Wassermann E, Thurnher M, Simunek M and Redl H: Skin graft fixation by slow clotting fibrin sealant applied as a thin layer. *Burns* 2006; 32: 305-11.

### *Effect of aprotinin source*

In relation to the change in the source of aprotinin (bovine to synthetic) for fibrin sealant, the seroma or haematoma formation and wound area healed at grafted sites observed on Days 7 and 14, respectively, were similar following application of fibrin sealant containing either source of aprotinin with 4 IU/mL thrombin (Tisseel VH S/D Kit 4 and Tisseel VH S/D synthetic aprotinin-containing (s-apr) Kit 4, both lyophilised, 0.05 mL/cm<sup>2</sup>). By Day 3 post-operation, haematoma formation (3.4% of total wound area) was slightly higher and take rate (96%) slightly lower in the synthetic aprotinin-containing fibrin sealant group, compared to the values (0% and 100%, respectively) in the bovine aprotinin-containing fibrin sealant group; however, the respective values were the same by Day 7 post-operation. There were no differences in foreign body reaction and inflammation at grafted sites between the two groups.

### *Effect of storage condition*

Furthermore, different storage conditions: deep freeze or lyophilisation of fibrin sealant containing 4 IU/mL thrombin (Tisseel VH S/D Duo 4 or Tisseel VH S/D Kit 4, respectively, 0.05 mL/cm<sup>2</sup>) did not contribute any differences to the above effects (0% seroma or 0-3.7% haematoma formation by Day 7 and 100% wound area healed by Day 14 post-operation).

### *Effect of solvent detergent treatment*

For viral inactivation, the solvent detergent (S/D) treatment of fibrin sealant (0.05 mL/cm<sup>2</sup>) did not cause any significant changes in the outcome at grafted sites. Interestingly, fibrin sealant without S/D treatment (Tisseel VH, lyophilised) tended to be slightly less effective than the S/D-treated one (Tisseel VH S/D Duo 4, deep frozen), based on the haematoma formation, take rate and wound area healed. The reason(s) for this might also include different product formulations and/or different storage conditions between these two products, but were not investigated further. However, the differences were small and are not considered biologically significant.

Overall, primary pharmacodynamic studies were limited to only one pig model. No tests were conducted directly on the proposed product and no *in vitro* comparability assays on inhibitory activities of synthetic and bovine aprotinin to serine proteases were performed. However, the study results of the pig model suggested that the efficacy of the proposed product (fibrin sealant containing 4 IU/mL thrombin and synthetic aprotinin, S/D treated and deep frozen) for adhesion of subcutaneous tissues was comparable to or better than that of suture for adhesion of autologous split skin grafts to surgically prepared wound beds in piglets. The fibrin sealant was easier for application, shorter in grafting time and had less foreign body reaction or inflammation than suture. In addition, the low dose (0.05 mL/cm<sup>2</sup>) was better than the high dose (0.15 mL/cm<sup>2</sup>) in terms of local tolerance. The deficiency of lacking *in vitro* assays on inhibitory activities of synthetic aprotinin to serine proteases for the fibrin sealant containing 4 IU/mL thrombin may be addressable by quality data (structures of the synthetic and bovine aprotinin and clot properties of fibrin sealants containing 4 IU/mL thrombin and synthetic aprotinin; see below) and clinical data.

## ***Haemostasis on subcutaneous tissue surfaces***

### *Effect of thrombin concentration*

Although fibrin sealants containing a high concentration (500 IU/mL) of thrombin (Tisseel Duo and Tisseel VH S/D) have been approved for haemostasis during surgical procedures, no nonclinical data were provided for haemostatic effects of fibrin sealants containing 4 IU/mL thrombin. This deficiency is addressable by clinical data.

*In vitro* studies comparing the structures of the synthetic and bovine aprotinin and clot properties (including clot lysis kinetics) of fibrin sealants formulated with the synthetic and bovine aprotinin were provided as quality data in the Tisseel application to change the source of aprotinin from synthetic to bovine and evaluated by the quality evaluator. Clotting time, tensile and adhesive strength of the clot, kinetics of aprotinin diffusion out of the clot, clot lysis kinetics and clot structure, and structures of the synthetic and bovine aprotinin were considered comparable between the synthetic and bovine aprotinin. These findings indicate the synthetic aprotinin does not alter clot properties of the sealant formulation containing a low concentration of thrombin (4 IU/mL), but did not demonstrate efficacy as an adjunct to haemostasis.

### **Secondary pharmacodynamics and safety pharmacology**

As indicated above, the compositions of Artiss are the same as those of the Tisseel VH S/D (deep frozen) registered in Australia, except for the lower thrombin concentration (4 IU/mL in Artiss compared with 500 IU/mL in Tisseel) and the source of aprotinin (synthetic in Artiss compared with bovine aprotinin in Tisseel). The maximum clinical dose of Artiss (40 mL/patient) is the same as for Tisseel VH S/D. The low concentration of thrombin in Artiss is not considered to be of safety concern.

Secondary pharmacodynamics, safety pharmacology, pharmacokinetics, and toxicity studies relating to the synthetic aprotinin are evaluated in a separate application.

In relation to the change in aprotinin source (bovine to synthetic), one study was submitted for comparability between synthetic and bovine aprotinin for bronchospastic activity, as an anaphylactoid reaction, in guinea pigs. No test article-related changes in the pulmonary inflation pressure from the baseline value (prior to treatment), in either the synthetic or bovine aprotinin group during the 10 minute recording period following intra-arterial administration of 20,000 KIU/kg. This indicates no anaphylactoid reactions by either source of aprotinin in this model. The intra-arterial dose of aprotinin by body surface area (BSA) ( $140,000 \text{ KIU/m}^2$ ) was 3.5-fold the maximum clinical dose at the surgical wound ( $39,600 \text{ KIU/m}^2$ )<sup>4</sup>.

No safety pharmacology studies on aprotinin or the finished product were provided. However, acute toxicity studies by intravenous (IV) injection at high doses (see below) showed no significant acute effects.

### **Pharmacokinetics**

The pharmacokinetic profile of synthetic aprotinin was similar to that of bovine aprotinin in mice at 500,000 KIU/kg by IV injection (both sources of aprotinin: the area under the plasma concentration time curve from time zero to infinity [ $AUC_{\infty}$ ] of 164-211 h·ng/mL, clearance 378-470 mL/h/kg, mean residential time 1.1-1.3 hours and half life 0.8-0.9 hours).

### **Toxicology**

#### **General toxicity**

The acute toxicity of synthetic and bovine aprotinin and the fibrin sealant containing these ingredients and 500 IU/mL thrombin was compared in mice, rats and rabbits by IV or subcutaneous (SC) injection.

In the single dose toxicity studies conducted in mice and rats, the animals received a single IV dose of synthetic aprotinin or bovine aprotinin at up to  $15 \times 10^5$  KIU/kg in mice and 8 x

<sup>4</sup> 40 mL fibrin sealant product (*sponsor's Nonclinical Overview*), equivalent to 0.8 mL/kg or 26 mL/m<sup>2</sup> (body surface area, BSA) sealant product for a 50 kg person and 39,600 KIU aprotinin/m<sup>2</sup>.

$10^5$  KIU/kg in rats. In both species, there were no notable changes in clinical observations, except for the behavioural depression, which was seen for up to 3 hours post-dose at all doses for both sources of aprotinin. In rats, dyspnoea and cyanosis were also seen for up to 1 hour post-dose in both aprotinin groups, at all doses in the synthetic aprotinin group and at high doses ( $\geq 400,000$  KIU/kg) in the bovine aprotinin group. In this species, body weight gains were lower at some doses in the synthetic aprotinin group, compared to the bovine aprotinin group, while the results were the opposite in mice. However both effects were not dose-related. Furthermore, there were no test article-related changes in the histopathological examination in both species at all doses. The highest IV doses of  $15 \times 10^5$  and  $8 \times 10^5$  KIU/kg (equivalent to  $45 \times 10^5$  and  $48 \times 10^5$  KIU/m<sup>2</sup>, respectively, in mice and rats) synthetic or bovine aprotinin were 114- and 121-fold the maximum clinical dose<sup>4</sup> applied to the surgical wound, respectively, on a BSA basis.

An acute SC toxicity study with Tisseel VH S/D s-apr Duo 500 containing 500 IU/mL thrombin and 3000 IU/mL synthetic aprotinin and Tisseel VH S/D Duo 500 containing the same amount of thrombin and bovine aprotinin in rats and rabbits showed no significant toxicity at 4 mL/animal (aprotinin dose: 20,000 KIU/kg in rats and 2000 KIU/kg in rabbits). In both species, body weight gains were greater (about 120-130%) in the fibrin sealant containing synthetic aprotinin group than in the product containing bovine aprotinin group for males, while the results were the opposite for females, and the overall results in both groups were therefore comparable. Although the administration route (SC injection) of the test articles in these animal studies was different from the clinical route of administration (local), the test dose of aprotinin in rats and rabbits (120,000 KIU/m<sup>2</sup> and 22,000 KIU/m<sup>2</sup>, respectively) was approximately 3- and 0.6-fold the maximum clinical dose based on BSA (39,600 KIU/m<sup>2</sup>), respectively.

The Sealer Protein Solution containing synthetic aprotinin was not cytotoxic to human embryonal diploid lung fibroblasts when cultured for about 30 minutes *in vitro*, although the cell culture period seemed to be too short to observe effects of the test item on cells.

No repeat dose toxicity studies were provided. It is expected that patients would be treated with Artiss on a single occasion. The safety of the synthetic aprotinin and products containing this ingredient from repeated use has not been adequately assessed by nonclinical studies.

### **Genotoxicity, carcinogenicity and reproductive toxicity**

In a bacterial gene mutation assay, the synthetic aprotinin was not genotoxic when tested using *Salmonella typhimurium* strains (detection of G-C and A-T mutations). Although the standard battery of genotoxicity studies have not been conducted, this is acceptable for a biological product that would not be expected to result in DNA modification.

No carcinogenicity or reproductive toxicity studies have been conducted, but this is also acceptable for this type of product (biological and subcutaneous use with single dose).

### **Use in children**

The efficacy and local tolerance of fibrin sealant containing 4 IU/mL thrombin and synthetic aprotinin were indirectly studied in piglets (about 3 months old), in relation to the proposed product (see *Primary pharmacodynamics*). No other toxicity studies were conducted on juvenile animals. According to the proposed Product Information, there seemed to be some clinical studies conducted on the paediatric population. Therefore, the adequacy of the proposed product for paediatric use relies on clinical data.

## Local tolerance

Local tolerance of the proposed product was investigated in the pharmacodynamic studies conducted for sealing of autologous split skin grafts in piglets. In these studies, the fibrin sealant containing 4 IU/mL thrombin and bovine aprotinin without S/D treatment did not have adverse effects at the grafted sites, except for mild foreign body reactions and mostly mild inflammation, which were expected from the exposure of heterologous proteins (human proteins to animals). The occurrence and/or severity of these reactions were lower in the fibrin sealant groups at doses tested up to 0.15 mL/m<sup>2</sup> than the suture group by Day 21 post-operation. The changes in the aprotinin source from bovine to synthetic and an addition of S/D treatment to the fibrin sealant did not influence the above effect.

No adverse effects were noted at the injection sites following a single IV or PV (paravenous) administration of synthetic aprotinin to rabbits.

In addition, there was no evidence of local toxicities of the fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin in rats and rabbits following subcutaneous implantation of decalcified bone spongiosa blocks with the test sealant. However, residual fibrin was greater for the sealant containing synthetic aprotinin than the product containing bovine aprotinin 14 days after application. The slower degradation of fibrin prepared from a fibrin sealant containing synthetic aprotinin than that prepared from a fibrin sealant containing bovine aprotinin suggests greater fibrinolysis inhibitory activity of the synthetic form than that of bovine aprotinin. Based on the animal study findings, fibrin at the surgical site treated with the synthetic aprotinin in patients may take longer to clear than the wound treated with bovine aprotinin. While this may not be a safety issue, it should be taken into consideration in the approval of this product.

## Immunogenicity

Neither synthetic nor bovine aprotinin had skin sensitising potential following intradermal and epidermal exposures to guinea pigs, but this assay assesses delayed hypersensitivity (Type IV allergic reactions) and may not predict acute anaphylactic reactions (Type I allergic reactions). The synthetic and bovine source of aprotinin did not show bronchospastic activity in guinea pigs following a single IV dose (see *Secondary pharmacodynamics and safety pharmacology*), suggesting the lack of acute anaphylactic effects, but the study did not include an induction phase, that is, prior exposure to synthetic aprotinin before a challenge dose of the compound. Antibodies to the synthetic aprotinin were not determined in any animal studies. The immunogenic potential of synthetic aprotinin has not been adequately evaluated in nonclinical studies. This is addressable by clinical data.

Anaphylactic or anaphylactoid reactions have been reported in patients treated with bovine aprotinin, and contraindication and precaution statements regarding potential anaphylactic reactions from aprotinin (bovine and synthetic) are included in the proposed Product Information.

## Nonclinical Summary and Conclusions

For adhesion of subcutaneous tissues, nonclinical studies were limited to one pig model. In this model, the efficacy of fibrin sealant (without S/D treatment and deep frozen) containing 4 IU/mL thrombin in the Thrombin Solution and bovine aprotinin was comparable to or slightly better than suture for adhesion of autologous split skin grafts to surgically prepared wound beds in piglets (about 3 months old). In addition, the fibrin sealant was easier for application, shorter in grafting time and had less foreign body reaction/inflammation than suture. The low dose (0.05 mL/cm<sup>2</sup>) performed better than the high dose (0.15 mL/cm<sup>2</sup>).

Synthetic aprotinin in replacement of bovine aprotinin did not alter the efficacy of the formulation in the pig model.

No *in vitro* comparability data on inhibitory activities of synthetic and bovine aprotinin to serine proteases were provided. This is considered a deficiency of the nonclinical section of the submission. However, comparability of the 4 IU/mL thrombin sealants containing synthetic and bovine aprotinin was demonstrated in the above pig model and in quality data. This deficiency does not preclude registration of the product provided clinical efficacy has been adequately demonstrated by clinical data.

In relation to the second indication proposed, no nonclinical data was provided for haemostatic effects of fibrin sealant containing 4 IU/mL thrombin. Therefore, the haemostatic efficacy of the proposed product on subcutaneous tissue surfaces relies on clinical data.

The pharmacokinetic profile of synthetic aprotinin was comparable to that of bovine aprotinin in mice following a single IV administration. In both aprotinin groups,  $AUC_{0-inf}$  was 164-211 h·mg/mL, clearance 378-470 mL/h/kg, mean residential time 1.1-1.3 hours and half life 0.8-0.9 hours.

In single dose toxicity studies, the effects of synthetic aprotinin were comparable to those of bovine aprotinin following a single IV administration to mice and rats. The doses tested were up to 114- and 121-fold the clinical dose, respectively, based on body surface area (BSA). The acute toxicity of Tisseel VH S/D s-apr Duo 500 (containing 500 IU/mL thrombin and synthetic aprotinin) were also comparable to those of Tisseel VH S/D Duo 500 (containing 500 IU/mL thrombin and bovine aprotinin) in rats and rabbits by the SC route at aprotinin doses of 3- and 0.6-fold the clinical dose (based on BSA), respectively. There were no repeat dose studies comparing the toxicity of synthetic and bovine aprotinin. Repeated use of the product is not supported by nonclinical data. The product should not be registered for repeated administration unless safety from repeated administration has been demonstrated by adequate clinical data.

The Sealer Protein Solution containing synthetic or bovine aprotinin was not cytotoxic to human embryonal diploid lung fibroblasts when cultured for around 30 minutes *in vitro*, although the cell culturing period was considered to be short. There was no evidence of genotoxicity of synthetic aprotinin in a bacterial reverse mutation test.

The local tolerance (granulation tissue formation, inflammation and foreign body reactions) of synthetic aprotinin (IV or perivenous) or Tisseel VH S/D s-apr Duo 500 was comparable to that of bovine aprotinin or Tisseel VH S/D Duo 500, respectively, in rats or rabbits. However, in both species the fibrin degradation treated with Tisseel VH S/D s-apr Duo 500 was slower than that with Tisseel VH S/D Duo 500 in a subcutaneously implanted spongiosa block model, suggesting greater fibrinolysis inhibitory activity of the synthetic aprotinin than bovine aprotinin and slower fibrin clearance at surgical wound treated with the fibrin sealant containing the synthetic aprotinin. This may not be a safety issue, but it should be taken into consideration in the approval of this product.

Neither synthetic nor bovine aprotinin had skin sensitising potential in guinea pigs, suggesting low potential for delayed hypersensitivity (Type IV allergic reactions) in patients. In a study for the bronchospastic activity as an anaphylactoid reaction using a guinea pig model, there were no test article-related changes in the pulmonary inflation pressure from the baseline value (prior to treatment), in either the synthetic or bovine aprotinin group during the 10 minute recording period. This indicates no respiratory anaphylactoid reactions from either source of aprotinin in this model. However, the study did not include an induction phase, that is, prior exposure to synthetic aprotinin before a challenge dose of the compound. Antibodies



to the synthetic aprotinin were not determined in any animal studies. The immunogenic potential of synthetic aprotinin has not been adequately evaluated in nonclinical studies.

The concentration of thrombin directly influences the speed of polymerization of the fibrin sealant: high concentration for instant clotting and low concentration for slow polymerisation. The fibrin sealant Tisseel VH S/D (deep frozen) containing a high concentration (500 IU/mL) of thrombin and bovine aprotinin has been registered since 2009 for instant clotting (haemostasis). Artiss is a variation of Tisseel VH S/D. Compared to the registered product, Artiss contains a lower concentration (4 IU/mL) of thrombin and synthetic aprotinin, and is indicated for tissue gluing (skin graft) and as an adjunct to haemostasis on subcutaneous tissue surfaces.

For the first indication (tissue gluing), although nonclinical studies were limited to one pig model, the efficacy of Artiss was considered to be comparable to or slightly better than that of suture for adhesion of autologous split skin grafts to surgically prepared wound beds in piglets. In addition, the fibrin sealant was easier to apply, shorter in grafting time and had less inflammation at grafted sites than suture. However, no nonclinical data was provided for the second indication (as an adjunct to haemostasis on subcutaneous tissue surfaces), and this is addressable by clinical data.

While a pharmacokinetic study, a cytotoxicity assay and single dose toxicity studies demonstrated comparability of the synthetic aprotinin with bovine aprotinin, the comparability of pharmacodynamics and immunogenicity were not sufficiently investigated. There were no studies on the inhibitory activities of the synthetic aprotinin to serine proteases such as plasmin, kallikrein and thrombin. Antibodies to synthetic aprotinin and anaphylactic reactions from repeated dosing were not studied. There were no repeat dose studies comparing the toxicity of synthetic and bovine aprotinin. The product should not be registered for repeated administration unless safety from repeated administration has been demonstrated by adequate clinical data. The absence of *in vitro* pharmacodynamic studies comparing the inhibitory activities of synthetic and bovine aprotinin to serine proteases does not preclude registration of the product provided clinical efficacy has been adequately demonstrated by clinical data.

Local tolerance studies in animal models suggest slower fibrin clearance at the surgical wound treated with the fibrin sealant containing the synthetic aprotinin than that treated with the sealant containing bovine aprotinin. While this may not be of a safety concern, it should be taken into consideration in the approval of this product.

## **IV. Clinical Findings**

### **Introduction**

A Phase I/II clinical study (clinical *study 520001*) that tested a commercially prepared, VH-treated, fibrin sealant with 4 IU/mL human thrombin (FS 4IU) was completed prior to a Phase III study of FS 4IU VH S/D (clinical *study 550201*).

FS 4IU VH S/D differs from FS 4IU in terms of an additional solvent/detergent (S/D) virus inactivation step, which was added to the manufacturing process to increase the potential safety profile of the product. The frozen presentation of FS 4IU VH S/D used in Baxter clinical study 550201 differs from that of the lyophilized form of FS 4IU in that it does not require reconstitution prior to product use; this product form was introduced to simplify the preparation process.

*Study 550201* was nominated by the sponsor as the pivotal efficacy and safety study, and it was stated that FS 4IU VH S/D is intended to adhere autologous skin grafts to surgically

prepared wound beds resulting from burns. The clinical program that investigated the use of FS 4IU VH S/D for this indication centred around clinical study 550201, a Phase III, multicentre, prospective, evaluator blinded, randomised study comparing FS 4IU VH S/D to staples for use in skin graft adherence and wound healing in subjects with burn wounds. The pivotal study was preceded by clinical study 520001, a Phase I/II, multicentre, prospective, randomised, comparative, feasibility study to assess the safety and efficacy of FS 4IU versus staples for wound healing through the facilitation of surgical closure.

Final clinical study reports were provided in the submission. The studies were conducted in accordance with Good Clinical Practice guidelines.

### **Pharmacokinetics and Pharmacodynamics**

No new pharmacokinetic or pharmacodynamic data were presented for evaluation.

### **Efficacy**

#### **Pivotal Study 550201**

This Phase III clinical study (550201) was designed to evaluate the safety and efficacy of a newly formulated 4 IU/mL thrombin fibrin sealant, FS 4IU VH S/D for use in adhering skin grafts and promoting wound healing in subjects with burn wounds.

The objectives of this study were to assess the safety and efficacy of FS 4IU VH S/D for skin graft adherence and wound healing in subjects with deep partial thickness or full thickness burn wounds. The primary efficacy objective was to test non-inferiority of FS 4IU VH S/D compared to the current standard of care (staples). Evaluation of complete (100%) wound closure by Day 28 should indicate whether the use of FS 4IU VH S/D in grafting procedures results in non-inferior graft adherence and wound healing when compared to the use of staples.

Study 550201 was a Phase III, multi-centre, prospective, evaluator blinded, randomised study comparing FS 4IU VH S/D to staples for use in skin graft adherence and wound healing in subjects with burn wounds. A schematic diagram of the study design is presented in Figure 2.

A total of 138 subjects were enrolled and treated in this study. Eligible subjects were required to have deep partial thickness or full thickness burn wounds that could be designated as a test area, and which could yield 2 comparable test sites. Each subject was to serve as his/her own control, receiving study product at one test site and staples at the other. The test sites were required to be either a single wound measuring between 2% and 8% total body surface area (TBSA) that could be split into 2 halves or 2 comparable, bilateral wounds each measuring between 1% and 4% TBSA. Both test sites were required to receive autologous sheet skin grafts with a thickness of 8/1000 of an inch to 16/1000 of an inch. Prior to randomisation, the wound beds were to be prepared for grafting and 2 test sites selected and labelled as Test site A and Test site B according to relative anatomical location. In accordance with the predetermined randomisation scheme, FS 4IU VH S/D was to be used to affix skin grafts at one test site (treatment), and staples used to affix skin grafts at the other test site (control). The randomisation envelopes were to be opened only after test site selection and wound bed preparation had occurred.

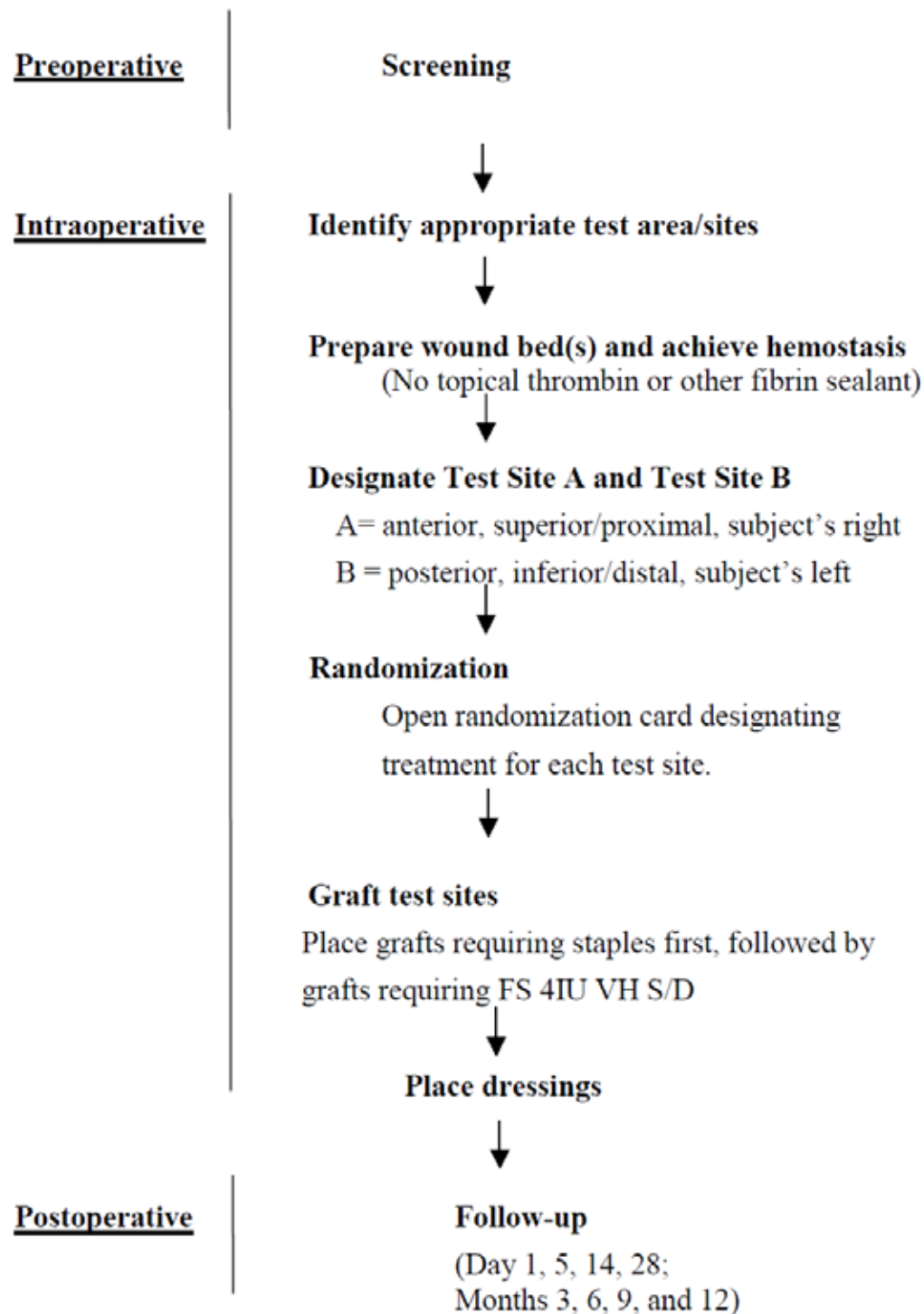
The postoperative follow-up was planned for 1 year. Subjects were required to undergo evaluations and study procedures at Screening and on Day 0, 5, 14, and 28 (Part A) and Month 3, 6, 9, and 12 visits (Part B). The postoperative assessments included observation/expression of haematoma/seroma, staple removal, assessment of graft viability (engraftment), assessment of wound closure, photography of the test sites, and investigator

and subject assessments of humanistic outcomes. Vancouver Scar Scale assessments were to be scheduled for Month 3, 6, 9, and 12 visits.<sup>5</sup>

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<sup>5</sup> The Vancouver Scar Scale is the standard scale used universally for scar assessment.

Figure 2: Study 550201 – Study Flowchart

*Efficacy Endpoints*Primary efficacy endpoint

The primary endpoint was complete wound closure by Day 28 after treatment with either FS 4IU VH S/D or staples as determined by a blinded independent review of the Day 28 photographs.

Secondary efficacy endpoints were as follows:

- Presence of haematoma/seroma on Day 1
- Percent area of haematoma/seroma on Day 1
- 100% engraftment by Day 5
- Percent area of engraftment on Day 5
- Complete wound closure by Day 14
- Percent area of closure by Days 14 and 28
- Scar maturation assessed by blinded Vancouver Scar Scale evaluations on Months 3, 6, 9, and 12.

The primary efficacy analysis was to be performed on the intent-to-treat and on the per-protocol population. The intent-to-treat population was to consist of all subjects with at least one available primary endpoint assessment. If in more than two cases the treatment and randomisation of sites differed, a second analysis of the intent-to-treat population was to be carried out in which the sites were analysed as they were randomized. This additional analysis was not required because randomisation did not differ in more than two cases.

*Study Population*

Treatment Populations

A list of inclusion and exclusion criteria was provided and considered appropriate.

The Intent-to Treat (ITT) and Per-protocol Populations (PP) were defined as follows:

Intent-to-treat population:

- If at least two assessors defined the picture as fully depicted and assessed the wound as closed, the site was to be defined as treatment success. All other combinations were to be defined as treatment failure.
- Regrafted sites were to be defined as failures.
- Sites with completely missing pictures were to be defined as treatment failure.
- Any detachment of grafts or non-adherence of grafts in any of the treatment sites was to be defined as failure.
- Additional staples or “Steri-Strips” placed after surgery (that is, later than Day 0) in any of the treatment sites was to be defined as failure.
- Staples not having been removed after Day 5 because of adherence problems was to be defined as failure.

Per-protocol population:

- If at least two assessors defined the picture as fully depicted and assessed the wound as closed, the site was to be defined as treatment success. All other combinations were to be defined as treatment failure.
- Regrafted sites were to be defined as failures.

- Any detachment of grafts or non-adherence of grafts in any of the treatment sites was to be defined as failure.
- Additional staples or “Steri-Strips” placed after surgery (that is, later than Day 0) in any of the treatment sites was to be defined as failure.
- Staples not having been removed after Day 5 because of adherence problems was to be defined as failure.

A total of 138 subjects were randomised and treated at 13 study sites. The number of subjects randomised at each study site ranged from 3 to 22. No single study site randomised a majority of subjects; therefore, site-specific bias is unlikely to have affected the results of this study. A total of 1525 burn patients were screened for eligibility according to the inclusion/exclusion criteria. Of the 1525 patients screened, 150 were enrolled into the study. In addition to the screen failures, there were 12 subjects who were enrolled but not randomised for one of the following reasons: 1) subject did not meet the eligibility criteria immediately prior to surgery (8 subjects); 2) investigator chose to use licensed Tisseel during surgery (1 subject); 3) subject’s wound became infected preoperatively (1 subject); 4) part of the test site was deemed by the investigator to be in a cosmetically inappropriate site on the face/neck (1 subject); and 5) study product was not available. Therefore, 138 of the 150 enrolled subjects were randomised. All 138 randomised subjects were treated at one test site with FS 4IU VH S/D and a separate test site with staples.

#### Demographic and Other Baseline Characteristics

Of the 138 treated subjects, 94 (68.1%) were male and 44 (31.9%) were female. The mean  $\pm$  SD (standard deviation) age was  $30.8 \pm 17.6$  years; 19 (13.8%) subjects were  $\leq 6$  years old, 21 (15.2%) subjects were 7 to 18 years old, and 98 (71.0%) were  $> 18$  years old.

In relation to burn wound characteristics for the safety population, of the 138 treated subjects, the mean  $\pm$  SD estimated TBSA for all burn wounds was  $13.6 \pm 9.2\%$ . The mean  $\pm$  SD estimated TBSA requiring skin grafting was  $8.0 \pm 6.9\%$ . The mean  $\pm$  SD estimated TBSA for the FS 4IU VH S/D test sites was  $1.7 \pm 0.8\%$  and for the stapled test sites was  $1.7 \pm 0.7\%$ .

For the safety population, burn wound thickness was classified as full thickness in 106 (76.8%) of the 138 treated subjects, and partial thickness in 32 (23.2%) subjects. The surgery was a one-stage process in 126 (91.3%) of cases, and two-stage in 12 (8.7%) of cases. The 2 selected test sites were contiguous (adjacent) in 111 (80.4%) subjects, and separate (non-adjacent) in 27 (19.6%) safety subjects.

Overall, the number of test sites located on specific anatomical areas was similar for FS 4IU VH S/D and stapled test sites for all populations. The most commonly grafted anatomical areas ( $>10\%$  of test sites) were right and left lower arms, and right and left lower legs for both FS 4IU VH S/D and stapled test sites.

#### *Efficacy Results*

##### Primary Efficacy Endpoint

The primary endpoint was complete wound closure by Day 28 after treatment with either FS 4IU VH S/D or staples, as determined by a blinded independent review of the Day 28 photographs. To prove non-inferiority of FS 4IU VH S/D compared to staples, the lower limit of the confidence interval (CI) of the difference between FS 4IU VH S/D and staples success rates had to be greater than  $-0.1$ .

Complete wound closure by Day 28 was achieved in 55 (43.3%) of the FS 4IU VH S/D test sites and 47 (37.0%) of the stapled test sites in the 127 ITT subjects. The lower limit of the 97.5% confidence interval of the difference between FS 4IU VH S/D and staples was  $-0.029$ . Therefore, FS 4IU VH S/D is non-inferior to staples at the 97.5% one-sided level for complete wound closure by Day 28 in the ITT population.

A similar result was obtained in the PP population: complete wound closure by Day 28 was achieved in 45.3% of the FS 4IU VH S/D test sites and 39.6% of the stapled test sites in the 106 PP subjects. The lower limit of the 97.5% confidence interval of the difference between FS 4IU VH S/D and staples was  $-0.041$ . Therefore, FS 4IU VH S/D was found to be non-inferior to staples in the ITT and PP populations at the 97.5% one-sided level for complete wound closure by Day 28 because the lower limit of the confidence interval of the difference between FS 4IU VH S/D and staples success rates was greater than the predefined limit of  $-0.1$ .

A number of prognostic factors were examined to investigate potential effects on the primary efficacy endpoint. Age, gender, wound depth (full versus partial thickness), wound size, wound location (extremities versus neck/torso), and number of dressing changes were examined using logistic regression. Gender, wound depth, and number of dressings did not have a significant effect on wound closure by Day 28 in FS 4IU VH S/D-treated or stapled test sites.

However, wound location appeared to have an effect on wound closure in FS 4IU VH S/D sites when extremities (hands, feet, arms, legs, shoulders and thighs) were compared to neck/torso (neck, chest, abdomen, back). Wounds located on extremities were less likely to achieve complete wound closure by Day 28 than wounds located on the neck/torso in FS 4IU VH S/D sites (odds ratio = 0.07; 95% CI for odds ratio = 0.01 to 0.37,  $p=0.0016$ ).

The reason for this apparent effect of wound location on wound closure at FS 4IU VH S/D sites is not clear; however, it is of note that the overall distribution of test site locations was uneven, with the majority of FS 4IU VH S/D test sites located on extremities ( $N=114$ ), rather than on the neck/torso ( $N=21$ ). In addition, the rate of wound closure on extremities was in the same range in FS 4IU VH S/D and stapled sites (37.3% vs. 35.1%, respectively in ITT subjects). Wound size may also have had a marginal effect on complete wound closure by Day 28 in FS 4IU VH S/D-treated sites (odds ratio = 0.49; 95% CI for odds ratio = 0.25 to 0.93,  $p=0.0291$ ). However, no effect of wound size on complete wound closure by Day 28 was observed in the stapled sites.

Logistic regression indicated that age might have had a marginal effect on complete wound closure by Day 28 in stapled sites. Complete wound closure by Day 28 occurred more often in younger subjects (odds ratio = 0.97; 95% CI for the odds ratio = 0.95 to 1.00,  $p=0.0305$ ). This effect was observed for both staples and FS 4IU VH S/D when different age groups were examined; the rate of complete wound closure by Day 28 was higher in the  $\leq 6$  years old group for both FS 4IU VH S/D and staples when compared to the 7 to 18 years old group or the  $>18$  years old group.

### Secondary Efficacy Outcomes

#### **Categorical efficacy endpoints**

The *categorical* secondary efficacy endpoints examined in study 550201 were as follows:

- Presence of hematoma/seroma on Day 1;
- 100% engraftment by Day 5; and

- Complete wound closure by Day 14.

The occurrence of haematoma/seroma on Day 1 was less frequent on FS 4IU VH S/D treated sites than stapled sites. In the ITT analysis, haematoma/seroma was present on Day 1 in 29.7% of the FS 4IU VH S/D-treated sites and 62.3% of the stapled sites ( $p = < 0.0001$ ). Engraftment on Day 5 was deemed to be 100% in 62.3% of the FS 4IU VH S/D-treated sites and 55.1% of the stapled sites ( $p = 0.0890$ ). Complete wound closure by Day 14 occurred in 48.8% of the FS 4IU VH S/D-treated sites and 42.6% of the stapled sites ( $p = 0.2299$ ). Outcomes of the categorical secondary endpoint variables for the PP population were similar.

The effects of various prognostic factors on the secondary efficacy outcome complete wound closure on Day 14 were also investigated. Wound depth was found to have a significant effect on complete wound closure by Day 14 in FS 4IU VH S/D-treated sites, whereas it did not in stapled sites. Full thickness wounds were less likely than partial thickness wounds to achieve complete wound closure by Day 14 in FS 4IU VH S/D-treated sites ( $p = 0.0040$ ). Despite this observation on Day 14, wound depth did not have a significant effect on complete wound closure by Day 28 in FS 4IU VH S/D-treated sites or stapled sites. The number of dressing changes may have had a marginal effect on complete wound closure on Day 14 in stapled sites ( $p = 0.0436$ ). Complete wound closure on Day 14 occurred more often in sites where more dressing changes were used, although the results were not conclusive. None of the other prognostic factors (age, gender, wound location, and wound size) investigated had a significant effect on the secondary efficacy outcome complete wound closure on Day 14.

### Continuous efficacy endpoints

The *continuous* secondary efficacy endpoints examined in study 550201 were as follows:

- Percent area of haematoma/seroma on Day 1;
- Percent area of engraftment on Day 5; and
- Percent area of closure by Days 14 and 28.

The continuous secondary endpoints were analysed twice: once without regrafted sites and sites that received additional staples, and once imputing a “worst case” result for regrafted sites and sites where additional staples were used.

Outcomes of the continuous secondary endpoint variables *without regrafted subjects* or subjects who received additional staples after surgery, for the ITT analysis were as follows:

The mean percent area of haematoma/seroma on Day 1 was lower in FS 4IU VH S/D-treated sites (0.7%) than in the stapled sites (4.6%). The median percent area of hematoma/seroma on Day 1 was 0.0% in FS 4IU VH S/D-treated sites and 1.2% in the stapled sites ( $p = < 0.0001$ ).

The mean percent area of engraftment on Day 5 was marginally higher in FS 4IU VH S/D-treated sites (97.5%) than in the stapled sites (96.5%). The median percent area of engraftment on Day 5 was 100.0% (95% CI = 100.0 to 100.0%; range: 34.4 to 100.0%) in FS 4IU VH S/D-treated sites and 100.0% (95% CI = 99.7 to 100.0%; range: 56.3 to 100.0%) in the stapled sites ( $p = 0.0250$ ).

The mean percent area of wound closure by Day 14 was marginally higher in FS 4IU VH S/D-treated sites (96.9%) than in the stapled sites (95.8%). The median percent area of wound closure by Day 14 was 100.0% in FS 4IU VH S/D-treated sites and 99.8% in the stapled sites ( $p = 0.0570$ ). The mean percent area of wound closure by Day 28 was marginally higher in FS 4IU VH S/D-treated sites (98.8%) than in the stapled sites (98.1%). The median percent area of wound closure by Day 28 was 100.0% (95% CI = 100.0 to 100.0%; range:



74.2 to 100.0%) in FS 4IU VH S/D-treated sites and 100.0% (95% CI = 100.0 to 100.0%; range: 78.1 to 100.0%) in the stapled sites ( $p= 0.0132$ ). Outcomes of the continuous secondary endpoint variables without regrafted subjects or subjects who received additional staples after surgery in the PP analysis were similar.

Outcomes of the continuous secondary endpoint variables *with regrafted subjects* or subjects who received additional staples after surgery included in the ITT analysis were as follows:

The mean percent area of haematoma/seroma on Day 1 was lower in FS 4IU VH S/D-treated sites (6.9%) than in the stapled sites (10.7%). The median percent area of haematoma/seroma on Day 1 was 0.0% in FS 4IU VH S/D-treated sites and 1.6% in the stapled sites ( $p< 0.0001$ ). The mean percent area of engraftment on Day 5 was similar in FS 4IU VH S/D-treated sites (91.3%) and stapled sites (90.6%).

The median percent area of engraftment on Day 5 was 100.0% in FS 4IU VH S/D-treated sites and 100.0% in the stapled sites ( $p= 0.0684$ ). The mean percent area of wound closure by Day 14 was similar in FS 4IU VH S/D-treated sites (90.5%) and stapled sites (89.6%). The median percent area of wound closure by Day 14 was 100.0% in FS 4IU VH S/D-treated sites and 99.3% in the stapled sites ( $p= 0.1092$ ). The mean percent area of wound closure by Day 28 was similar in FS 4IU VH S/D-treated sites (92.4%) and stapled sites (91.9%). The median percent area of wound closure by Day 28 was 100.0% in FS 4IU VH S/D-treated sites and 100.0% in the stapled sites ( $p= 0.0950$ ).

Outcomes of the continuous secondary endpoint variables with regrafted subjects or subjects who received additional staples after surgery included in the PP analysis were similar.

### **Humanistic Outcomes**

A number of subject- and investigator-reported outcomes were investigated during the Baxter clinical study 550201. The mean pain score reported by subjects was significantly higher immediately after staple removal than that assessed immediately before staple removal. In addition, subjects reported less anxiety about pain with FS 4IU VH S/D than with staples on Day 14. Overall, subjects had a significant preference for FS 4IU VH S/D over staples as assessed on Day 5, Day 14 and Day 28.

Assessment of preference on Day 5 revealed that 64.8% (59/91) of subjects “Strongly prefer glue [FS 4IU VH S/D]” and 18.7% (17/91) of subjects “Somewhat prefer glue”. Overall, there was a significant preference for FS 4IU VH S/D over staples on Day 5 ( $p= <0.0001$ ). The results of the same assessment of preference on Day 14 and Day 28 revealed similar results. Again, there was a significant preference for FS 4IU VH S/D over staples on Day 14 and Day 28 ( $p= <0.0001$ ).

Investigators also assessed graft adherence quality. The mean score on Day 0 and Day 5 was significantly higher for FS 4IU VH S/D than staples. Investigators were also asked to rate their fixation method of preference for each procedure on Day 14 and Day 28. The investigators indicated a significant preference for FS 4IU VH S/D over staples on Day 14 and Day 28.

In addition, investigators were significantly more satisfied with the graft fixation provided by FS 4IU VH S/D compared with staples on Day 14 and Day 28 ( $p< 0.0001$ ). Investigators were significantly more satisfied with the overall quality of healing in the FS 4IU VH S/D sites than the stapled sites on Day 14 and Day 28. The level of satisfaction with the overall rate of healing as assessed by the investigators was also significantly higher in the FS 4IU VH S/D sites than the stapled sites on Day 14 and Day 28.

*Evaluator Comment*

The primary efficacy endpoint for study 550201 was met demonstrating that FS 4IU VH S/D is efficacious when used to adhere autologous skin grafts to surgically prepared wound beds resulting from burns. Secondary efficacy results also confirmed efficacy of FS 4IU VH S/d in terms of adhering skin grafts and promoting wound healing in subjects with burn wounds. Humanistic outcomes supported the use of FS 4IU VH S/D in skin grafting procedures. The results cannot necessarily be extrapolated to other populations of patients.

**Supportive Study 520001**

This was a Phase I/II, multicentre, prospective, randomised, comparative, feasibility study to assess the safety and efficacy of FS 4IU for wound healing through the facilitation of surgical closure in subjects with burn wounds requiring autologous, split-thickness, sheet skin grafts. A total of 40 subjects were enrolled in this study. Subjects had to have burn wounds measuring  $\leq 40\%$  of total body surface area (TBSA) that included test areas comprising, a) either a single contiguous wound area (test area) measuring between 2% and 8% TBSA that could be divided into 2 approximate halves, or b) 2 bilateral wounds (each measuring between 1% and 4% TBSA). All test sites were either deep partial thickness or full thickness wounds. Digits, head, genitalia, palms of hands, soles of feet, and face were excluded. According to a predetermined randomisation scheme, one test site had sheet skin grafts affixed with FS 4IU (treatment) and the other test site had sheet skin grafts affixed with staples (control), allowing each subject to serve as his/her own control.

Study 520001 was composed of 2 study periods: 1) An initial 3-month follow-up for all subjects; 2) A 9-month extension for all subjects who achieved surgical closure in one or both test sites. Postoperative study procedures and assessments for the 3-month follow-up were performed on Days 1, 5, 14, 21, 28, 35, 49, 64, and 91. These assessments included vital signs, planimetry, surgical closure, observations of haematoma and seroma formation, questionable viability, overall graft survival, photography, and the investigators' clinical impressions (categories of pigmentation, vascularity, and pliability). Days 28, 35, 49, and 64 were optional visits for subjects who achieved surgical closure in both of their test sites by Day 21. If surgical closure was not achieved in one or both of the test sites on the Day 21 visit, the subject returned for visits on Days 28, 35, 49, and 64 until surgical closure was achieved. Subjects who achieved surgical closure in one or both of their test sites within the 3-month follow-up period were eligible to enter the 9-month extension. Subjects continuing in the 9-month extension were evaluated at 6, 9 and 12 months after surgery using photography, the Vancouver Scar Scale, and other scar assessments including keloid formation and hypertrophic scarring.

Objectives were as follows:

1. To evaluate the adherence properties of FS 4IU when applied to autologous split-thickness, sheet skin grafts compared with the current standard of care for skin graft fixation (staples);
2. To compare graft survival (% area) of wounds affixed with FS 4IU to those affixed with staples;
3. To compare surgical closure for grafts affixed with FS 4IU to those affixed with staples;
4. To compare areas of questionable viability (% area) for grafts affixed with FS 4IU to those affixed with staples;
5. To evaluate hematomas, seromas, and contracture affixed with the use of FS 4IU and staples;

6. To evaluate the effects associated with the staple removal process; and
7. To evaluate the overall safety of FS 4IU used in skin grafting surgery.

### *Efficacy Endpoints*

Efficacy was evaluated by the following:

1. Investigator's assessment of the adherence of FS 4IU on Day 0 using a 4-point scale (excellent, good, fair, poor).
2. Haematoma and seroma formation (% area) on Day 1.
3. Number of haematomas and seromas on Day 1.
4. Questionable viability (% area) on Day 5.
5. Staple removal measures on Day 5.
6. Overall graft survival (% area) on Day 14.
7. Proportion of subjects achieving surgical closure on Day 5.
8. Time to surgical closure.
9. Frequency, cumulative frequency, and cumulative percent of subjects with surgical closure at each test site, assessed at each visit.
10. Investigators' clinical impressions of pigmentation, vascularisation, and pliability on Days 5, 14, 21, 28, 35, 49, 64, and 91.
11. Degree of contracture on Days 5, 14, 21, and 91.
12. Rate of regrafting.
13. Vancouver Scar Scale assessments at 6, 9, and 12 months after surgery.
14. Incidence of keloid formation and hypertrophic scarring.

### *Study Population*

The main criteria for inclusion were that subjects were to have total burn wounds measuring  $\leq 40\%$  of TBSA that included either: a) a single contiguous wound area (test area) measuring between 2% and 8% TBSA that could be divided into 2 comparable test sites for grafting; or b) 2 bilateral wounds, each measuring between 1% and 4% TBSA.

Of the 40 treated subjects in study 520001, 72.5% were male and 27.5% were female. Race/ethnicity was 67.5% Caucasian, 22.5% Hispanic, and 10.0% Black. The mean age ( $\pm$  SD) was 30.5 ( $\pm$  14.2) years, and the median age was 32.7 (range: 6.2 to 54.6) years. Of the 40 treated subjects, 7.5% were  $\leq 6$  years old, 15.0% were 7 to 18 years old, and 77.5% were  $>18$  years old. The mean weight ( $\pm$  SD) was 68.1 ( $\pm$  23.7) kg and the mean height ( $\pm$  SD) was 165.1 ( $\pm$  20.9) cm. The estimated mean TBSA  $\pm$  SD for all burn wounds was  $15.6 \pm 9.62\%$  (range: 3 to 40%). The estimated mean TBSA  $\pm$  SD for each subject's entire test area (both test sites) was  $3.2 \pm 1.26\%$  (range: 2 to 8%). Twenty-six (65%) subjects had full thickness burn wounds and 14 (35%) subjects had partial thickness burn wounds.

### *Efficacy Results*

The adherence of skin grafts on FS 4IU-treated sites on Day 0 was rated as excellent or good by the investigator in all but one subject. The median percent area of haematoma and seroma formation on Day 1 was significantly less ( $p = 0.0138$ ) for the FS 4IU-treated sites (0.0%) than for the stapled sites (2.1%), indicating that at least 50% of the FS 4IU-treated sites had

no areas of haematoma and seroma formation. The median percent area of questionable viability was significantly less ( $p = 0.0182$ ) for the FS 4IU-treated sites (0.0%) than for the stapled sites (0.5%) on Day 5, indicating that at least 50% of the subjects with FS 4IU-treated sites had no areas of questionable viability by Day 5. A higher degree of contracture was observed for FS 4IU-treated sites compared with stapled sites ( $p = 0.0094$ ) on Day 5. No differences in degree of contracture were observed for the two test sites on Days 14, 21, or 91. Investigators' clinical impressions of pigmentation, vascularisation, and pliability were similar for both treatments; pigmentation was normal in a nearly identical proportion of subjects over time, while both (normal) vascularisation and pliability increased in a similar proportion of subjects from Day 5 to Day 91.

The median number of staples used per subject was 30 and the median time spent removing staples was 10 minutes. Supplemental pain medication was required in 29.7% of subjects during the staple removal procedure; these subjects had already received background pain medication/sedation treatment prior to the start of staple removal. The median pain score (on a scale of 0 to 5) immediately before staple removal was 2 (1 subject reported  $> 5$ ) and immediately after staple removal was 4 (5 subjects reported  $> 5$ ).

The median percent area of overall graft survival on Day 14 was 100.0% for both sites ( $p = 0.3525$ ), and the percentage of subjects deemed surgically closed at Day 5 was not statistically different between the groups ( $p = 0.0703$ ). The median time to surgical closure was 5 days for both treatments ( $p = 0.2383$ ). In addition, more FS 4IU-treated sites ( $N = 37$ ) closed by Day 91 compared to the corresponding stapled sites ( $N = 32$ ), and the FS 4IU-treated sites closed sooner than the stapled sites. On Day 5, FS 4IU-treated sites were closed in 61.5% of the subjects, whereas stapled sites were closed in only 46.2% of subjects ( $p = 0.0703$ ). The maximum difference occurred at the Day 28 visit; therefore, a paired analysis was performed on the Day 28 data. Wound closure by Day 28 was achieved in 79.5% of FS 4IU-treated sites compared with 59.0% stapled sites, a statistically significant difference ( $p = 0.0215$ ).

Vancouver Scar Scale assessments of pigmentation, vascularity, pliability, and height, in addition to keloid formation and hypertrophic scarring assessments were completed postoperatively at Month 6, Month 9, and Month 12 by the investigators. No statistically significant differences between FS 4IU-treated sites and stapled sites were found for any of the Vancouver Scar Scale properties evaluated at the 6, 9, or 12 month visits. In addition, no statistically significant differences between FS 4IU-treated sites and stapled sites were found for the assessments of keloid formation and hypertrophic scarring evaluated at the 6, 9, or 12 month visits.

### **Comparison of Analyses of Results Across Studies**

The outcomes of Baxter clinical study 520001 and Baxter clinical study 550201 concurred in terms of presence of haematoma/seroma on Day 1, with both studies observing a significantly lower incidence for the study product (FS 4IU or FS 4IU VH S/D) versus staples. In contrast, the statistical conclusions were different between the 2 studies in terms of complete wound closure on Day 28, complete wound closure on Day 14, and 100% engraftment on Day 5. The different outcomes from the two studies for complete wound closure on Day 28 may be due to the two different methods of assessment for this endpoint. Complete wound closure on Day 28 was assessed by the investigator during physical examination of the test site during study 520001, whereas it was assessed by a blinded review of photographs in study 550201. The rate of complete wound closure on Day 28 was lower for both treatments (FS 4IU VH S/D and staples) in study 550201 compared with Baxter clinical study 520001. This may be

due to the strict operational definition of complete wound closure on Day 28 employed in study 550201, which may have resulted in a more conservative outcome for both treatments than would be expected at this time point.

In addition, the significant difference between FS 4IU and staples observed in Baxter clinical study 520001 was not replicated in Baxter clinical study 550201, and this may be partly explained by the removal of bias by the blinded review of the Day 28 photographs.

Despite the different outcomes for this efficacy endpoint, the non-inferiority of FS 4IU VH S/D compared to staples is supported by the results of both studies.

#### *Evaluator Comment*

Overall, the categorical outcomes of study 550201 should be given greater weight over those of study 520001 because of the larger sample size and the use of a blinded independent review panel for the assessment of the primary endpoint (complete wound closure on Day 28). Despite the differences observed, the two studies both support the use of FS 4IU VH S/D to adhere autologous skin grafts to surgically prepared wound beds resulting from burns.

The analysis of the continuous efficacy endpoints for study 520001 (without regrafted subjects) and study 550201 (without regrafted subjects and subjects who received additional staples) revealed a very similar outcome. The lack of major differences between the results of the two studies supports the validity of the quantitative assessments used to compare the two treatments.

#### *Comparison of Results in Subpopulations*

A fully integrated analysis of subpopulations was not done due to the limited sample size of study 520001, and the use of different methods (investigator assessed versus blinded review) to assess the primary endpoint (complete wound closure on Day 28). However, the primary endpoint of Baxter clinical study 550201 (complete wound closure on Day 28) was analysed according to the following age groups:  $\leq 6$  years old, 7 to 18 years old, and  $> 18$  years old. Complete wound closure on Day 28 in the  $\leq 6$  years old group occurred in 72.2% (13/18) FS 4IU VH S/D-treated sites and 72.2% (13/18) stapled sites. By comparison, complete wound closure on Day 28 in the 7 to 18 years old group occurred in 31.6% (6/19) FS 4IU VH S/D-treated sites and 26.3% (5/19) stapled sites. Similarly, complete wound closure on Day 28 in the  $> 18$  years old group occurred in 40.0% (36/90) FS 4IU VH S/D-treated sites and 32.2% (29/90) stapled sites. These results support the use of FS 4IU VH S/D in the paediatric population, and highlight the interesting observation that the rate of complete wound closure on Day 28 is higher in the  $\leq 6$  years old group than the 7 to 18 years old or  $> 18$  years old groups regardless of the treatment (FS 4IU VH S/D or staples) received. This higher rate of complete wound closure for both FS 4IU VH S/D and staples in younger subjects is not unexpected based on the widely accepted fact that the rate of wound healing in children is faster than in adults.

#### **Efficacy Conclusions**

Results from studies 550201 and 520001 showed that FS 4IU VH S/D was efficacious when used to adhere skin grafts in burn wounds. In the pivotal study 550201 only patients with burn wounds were treated.

The sponsor's proposed indication is as follows:

*Artiss is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery. 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.*

*In addition, Artiss is proposed to be indicated as an adjunct to haemostasis on subcutaneous tissue surfaces, for example in the procedures mentioned above.*

In the proposed indication, patients undergoing reconstructive and plastic surgery are included in the population to be treated. In addition the sponsor proposes that Artiss be used to replace sutures in other clinical conditions. No data have been presented for patients treated in these other clinical circumstances. The evaluator therefore considered that the efficacy data were not sufficient to support use in indications other than treatment to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and paediatric populations.

The studies submitted for evaluation showed that FS 4IU VH S/D does reduce the incidence and extent of haematoma and seroma compared to that observed with the current standard of care (staples). This however only applied in the patients treated in the studies (burns wounds), and therefore these results cannot be extrapolated to other populations and clinical settings. It was therefore considered that the efficacy data were not sufficient to support that Artiss should be indicated as an adjunct to haemostasis on subcutaneous tissue surfaces in the procedures mentioned in the proposed indication.

## **Safety**

### **Study 550201**

A total of 433 adverse effects (AEs) occurred in 120 subjects during Part A (up to and including Day 28) of study 550201. Of the 433 AEs, 15 in 12 (8.7%) subjects were serious adverse experiences (SAEs). None of the 15 SAEs was considered related to FS 4IU VH S/D.

Graft loss resulting from infection or from mechanical forces constituted the most frequently occurring type of SAE in this study at both test sites and non-test sites. Of the SAEs occurring at test sites, 3 incidences of infection and 1 incidence of staphylococcal infection occurred at both the FS 4IU VH S/D test site and the stapled test site. There were also 4 incidences of skin graft failure occurring at the FS 4IU VH S/D test site and 3 incidences at the stapled site. In all cases, skin graft failure was due to infection or mechanical forces (scratching or shearing). None of the SAEs occurring in either the FS 4IU VH S/D test site or the stapled test site was considered related to FS 4IU VH S/D by the investigator. Likewise, none of the non-test site SAEs was considered related to FS 4IU VH S/D.

A total of 418 non-serious AEs occurred in 117 (84.8%) subjects. A similar incidence of non-serious AEs occurred at FS 4IU VH S/D and stapled test sites, except for a larger incidence of graft complication at the stapled test sites (15 versus 2 incidences in FS 4IU VH S/D test sites); 12 of the 15 graft complications were due to retained staples.

Eight of the non-serious AEs were deemed related to FS 4IU VH S/D by the investigator. Of the 8 related non-serious AEs, 5 were incidences of skin graft failure: 2 were graft slippage/graft detachment occurring on Day 1; 2 were graft detachment/non-adherence occurring on Day 2; and 1 was graft necrosis occurring at Day 16. The graft detachment in two of the subjects may have been related to the maximum thawing temperature (40°C) being exceeded during the study product preparation. In addition, all 4 subjects with graft slippage/detachment/non-adherence received doses of FS 4IU VH S/D below the recommended dosing volume of 2 to 4 mL/100cm<sup>2</sup>, and this fact may also have contributed to

the lack of graft adherence. The three other non-serious AEs considered related to FS 4IU VH S/D were 2 incidences of pruritus and 1 incidence of dermal cyst.

The most common (> 10 incidences) non-serious AEs not occurring at test sites were pruritus (45), constipation (34), insomnia (16), pyrexia (12), haemoglobin decreased (12), and nausea (11). None of the non-serious AEs not occurring at test sites were considered related to the use of FS 4IU VH S/D.

In terms of the AEs that occurred in  $\geq 5\%$  of subjects, a similar rate of infection AEs occurred on the FS 4IU VH S/D test site (4.3%) compared with stapled test sites (5.1%). However, a higher rate of graft complication occurred in stapled test sites (10.1%) compared with FS 4IU VH S/D test sites (1.4%). The majority of these graft complications were the result of retained staples. The rates of skin graft failure were similar between FS 4IU VH S/D test sites (25.4%) and stapled test sites (23.2%).

Likewise, the rates of pruritus were similar between FS 4IU VH S/D test sites (20.3%) and stapled test sites (21.0%).

Examination of vital signs on the day of surgery did not reveal safety concerns for FS 4IU VH S/D.

### **Study 520001**

A total of 423 adverse experiences were reported in 40 subjects during the entire 12 month period of study 520001. Among these, 6 (1.4%) events in 3 subjects were serious and 417 (98.6%) events in 40 subjects were non-serious. There were no deaths. None of these serious adverse experiences were considered related to the use of FS 4IU. Five of the serious adverse experiences were reported in two subjects and were rated moderate; the remaining serious adverse experience was rated severe.

Of the non-serious, 296 (70.0%) adverse experiences reported in 37 subjects were rated mild, 116 (27.4%) in 26 subjects were rated moderate, and 5 (1.2%) in 5 subjects were rated severe. Of the reported adverse experiences, 6 (1.4%) were judged by the investigators to be possibly related to the use of FS 4IU. Five of the 6 were cases of hematoma and seroma in the FS 4IU-treated sites and were reported by a single investigator. By contrast, no other investigators reported hematoma and seroma as study product-related.

The remaining 417 (98.6%) adverse experiences were judged by the investigators to be unrelated. Seventeen types of events (abscess, blister, cellulitis, excoriation, folliculitis, graft complication, graft loss, hematoma, hypertrophic scar, limb injury, muscle cramp, pain, pain in extremity, pruritus, seroma, staphylococcal infection and stitch abscess) were reported to have occurred locally at one or both test sites. Among these event types, there was no apparent difference in the frequency of occurrence at FS 4IU-treated or stapled sites. A total of 75 events were localised to FS 4IU-treated sites and 92 were localised to stapled sites.

Examination of vital signs, haematology, and clinical chemistry parameters did not reveal safety concerns for FS 4IU.

### **Deaths**

There were no deaths during study 550201 or 520001.

### **Other Significant Adverse Events**

There were no marked haematological or other laboratory abnormalities, or events that led to a substantial intervention in either of the two studies.

## Evaluator Comment

Overall data from the two clinical studies showed no major safety concerns in relation to use of FS 4IU VH S/D.

## Clinical Summary and Conclusions

In this application the sponsor is seeking registration of Artiss Fibrin Sealant VH S/D 4 IU (Frozen). The indication proposed by the sponsor is as follows:

*Artiss is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery. 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.*

*In addition, Artiss is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces, for example in the procedures mentioned above.*

Study 550201 was the pivotal efficacy and safety study. This was a Phase 3, multicentre, prospective, evaluator blinded, randomised study comparing FS 4IU VH S/D to staples for use in skin graft adherence and wound healing in subjects with burn wounds. The pivotal study was preceded by clinical study 520001, a Phase I/II, multicentre, prospective, randomised, comparative, feasibility study to assess the safety and efficacy of FS 4IU versus staples for wound healing through the facilitation of surgical closure.

Results from studies 550201 and 520001 showed that FS 4IU VH S/D was efficacious when used to adhere skin grafts in burn wounds. The primary efficacy endpoint for study 550201 was met demonstrating that FS 4IU VH S/D is efficacious when used to adhere autologous skin grafts to surgically prepared wound beds resulting from burns. Secondary efficacy results also confirmed efficacy of FS 4IU VH S/d in terms of adhering skin grafts and promoting wound healing in subjects with burn wounds. Humanistic outcomes supported the use of FS 4IU VH S/D in skin grafting procedures.

In the pivotal study 550201 only patients with burn wounds were treated, and results cannot be extrapolated to use of the sealant in other clinical settings. In the proposed indication, patients undergoing reconstructive and plastic surgery are included in the population to be treated. In addition the sponsor proposes that Artiss be used to replace sutures in other clinical conditions. No data have been presented for patients treated in these other clinical circumstances. The evaluator therefore considered that the efficacy data were not sufficient to support use in indications other than treatment to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and paediatric populations.

The studies submitted for evaluation showed that FS 4IU VH S/D does reduce the incidence and extent of haematoma and seroma compared to that observed with the current standard of care (staples). This however only applied in the patients treated in the studies (burns wounds), and therefore these results cannot be extrapolated to other populations and clinical settings. It was therefore considered that the efficacy data were not sufficient to support that Artiss should be indicated as an adjunct to haemostasis on subcutaneous tissue surfaces in the procedures mentioned in the proposed indication.

The indication should be modified to reflect this.

It was recommended that the application for registration of Artiss should be approved but the indication should be amended to reflect that it should only be used to adhere skin grafts to surgically prepared wound beds resulting from burns.



An indication similar to the approved indication in the US should be considered. This is as follows:

*Artiss is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and paediatric populations. Artiss is not indicated for haemostasis.*

## **V. Pharmacovigilance Findings**

### **Risk Management Plan**

A risk management plan (RMP) was submitted in support of this application, and the following important safety concerns were identified by the sponsor:

Important identified risks:

- Allergic reactions
- Intravascular application

Important potential risks:

- Risk of viral transmission
- Granulation tissue formation, residual fibrin, inflammation and foreign body reaction as well as skin induration

Important missing information:

- Interaction with other medicinal products; Incompatibilities
- Preclinical studies regarding subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation

The RMP was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM) and it was noted that the sponsor proposed application of routine pharmacovigilance activities for all safety concerns as identified by the sponsor. This was considered generally acceptable.

In addition the sponsor has acknowledged that the safety profile of fibrin sealant is unknown in pregnant or lactating women or in patients with immunodeficiency and/or pre-existing haemolytic anaemia. It was noted that there were no provisions in the pharmacovigilance plan to pro-actively obtain information regarding the incidence and nature of adverse drug events (ADEs) in these groups.

It was acknowledged that use of fibrin sealant in these groups was either not recommended (although not contraindicated) or a circumstance where caution was required with its use. Nevertheless it was suggested that routine pharmacovigilance is insufficient with respect to gathering information on the safety profile of fibrin sealant in each of these specified patient groups. Therefore it was suggested the sponsor makes some provision to pro-actively gain such information. This may take the form of a patient register, the details of which should be agreed with the TGA.

Based on the evaluation of the need for risk minimisation activities, the sponsor has concluded that routine risk minimisation activities are sufficient for all the identified safety concerns. The proposed application of routine risk minimisation activities to the safety concerns, as specified by the sponsor, was considered acceptable.

In regard to off-label use, it has been reported that fibrin sealants have been used to reinforce muscular support for intracranial saccular aneurysms. The sponsor should comment on such off-label use and the associated potential risks, if any.

## **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

The process validation performed previously for Tisseel is applicable to the bulks and Sealer Protein Solution in Artiss.

The Thrombin Solution in Artiss is manufactured by a similar process to that of the Thrombin Solution in Tisseel except that the Thrombin Bulk is diluted to a target concentration of 4.2 IU/mL. Process validation was satisfactory. The release specifications comply with the Ph. Eur.. Viral and prion safety were acceptable.

There were no objections to registration. The TGA will require initial batch monitoring until the consistency of the product is demonstrated.

### **Nonclinical**

Artiss was comparable to sutures for adhesion of autologous split skin grafts to surgically prepared wound beds in piglets. There were no data on the use of Artiss as an adjunct to haemostasis.

No toxicity was evident in single-dose, local tolerance or genotoxicity studies.

The evaluator supported approval subject to clinical data.

### **Clinical**

The pivotal study 550201 was a randomised controlled trial in 138 burns subjects undergoing autologous skin grafts. Two comparable test sites were identified in each subject and the sites were randomly allocated either Artiss or staples for graft adherence. Of the randomised subjects, 127 were evaluable in the modified intent-to-treat analysis which included subjects with at least one primary endpoint assessment. The median age of subjects was 31 years, range 1-62 years. 14% were  $\leq 6$  years of age and 15% 7-18 years of age. 66% were male. Similar areas were treated at the two sites: mean  $\pm$  SD  $1.7 \pm 0.8\%$  body surface area at Artiss sites and  $1.7 \pm 0.7\%$  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.

The primary endpoint was complete wound closure by Day 28 as determined by blinded independent review. Secondary endpoints were assessed by investigators. Artiss was non-inferior to staples in complete wound closure by Day 28 in the modified intent-to-treat analysis (Table 2). A similar result was obtained in the per protocol analysis. The non-inferiority criterion was a lower limit of the 97.5% confidence interval of the difference between treatments  $> -0.1\%$ . There was support from secondary endpoints (Table 2).

Table 2: Artiss Efficacy in Trial 550201 – Modified Intent-to-Treat

<b>Endpoint</b>	<b>Artiss</b> n=127	<b>Staples</b> n=127	<b>Difference</b> <b>[95% CI]</b>
Complete wound closure by day 28 <sup>1</sup>	43.3%	37.0%	6.3% [-2.9%, 15.5%] 97.5% CI: [-0.03%, -]
Complete wound closure by day 14 <sup>2</sup>	48.8%	42.6%	6.2% [-2.6%, 15.0%]
Haematoma/seroma on day 1 <sup>2</sup>	29.7%	62.3%	-32.6% [-41.4%, -23.8%]
Engraftment 100% by day 5 <sup>2</sup>	62.3%	55.1%	7.2% [-0.2%, 14.7%]

<sup>1</sup> Assessed by blinded review panel. <sup>2</sup> Assessed by investigator.

Study 520001, a pilot study of an earlier version of Artiss in 40 subjects, was supportive of the non-inferiority of Artiss to staples in wound closure after autologous skin grafting.

There was a high incidence of adverse events in both trials (87% in the pivotal study and 100% in the pilot study). The majority of events were considered unrelated to treatment. The incidence of skin graft failure was similar for the two treatments in the pivotal trial (25% for Artiss and 23% for staples); however, graft complications were lower with Artiss (1.4% for Artiss versus 10% for staples). The incidence of infection was similar (4.3% for Artiss and 5.1% for staples) as was pruritus (20% for Artiss and 21% for staples). Eight events were considered related to Artiss, five of skin graft failure (3.6%), two of pruritus (1.4%) and one of dermal cyst (0.7%). In the pilot trial, four events were considered related to Artiss, two of haematoma (5.0%), one of seroma (2.5%) and one of skin graft failure (2.5%).

The evaluator recommended approval with the indication limited to the population in the trials.

### **Risk Management Plan**

The Risk Management Plan submitted with the application was acceptable.

The Delegate agreed with the sponsor that a patient register or other measures are not necessary to clarify the safety of Artiss in pregnant and lactating women and patients with immunodeficiency or haemolytic anaemia.

### **Risk-Benefit Analysis**

Artiss was non-inferior to staples, a standard method of graft adherence, in complete wound closure by Day 28 in burns subjects undergoing autologous skin grafts. There was support from secondary endpoints. The safety profiles of the two treatments were generally similar. There were no data for other plastic and reconstructive surgery procedures including skin flaps, no data on the use of Artiss to replace sutures or as an adjunct to sutures and no data on Artiss as an adjunct to haemostasis in these procedures.

The Delegate supported the clinical evaluator in recommending the indication be limited to the population in the trials.

The Delegate recommended approval for the following indication:

*Artiss is indicated to adhere autologous skin grafts in burns patients. Artiss is not indicated for haemostasis.*

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission for the indication:

*For use in adhering autologous skin grafts in burns patients. Artiss is not indicated for haemostasis.*

In making this recommendation, the ACPM noted that the evidence submitted was relevant only to use in the treatment of burns and agreed with the Delegate that the safety and efficacy evidence supported the registration of this product for the above indication. In addition, the ACPM noted that the data were too limited to support the claim that Artiss reduced the incidence of haematoma and seroma, in particular, in clinical study 550201, it was not clear if both the incidence of haematoma and seroma were reduced over the whole healing period.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Artiss solution syringe containing fibrin sealant VH S/D 4IU (frozen) for the indication:

*Artiss is indicated to adhere autologous skin grafts in burns patients. Artiss is not indicated for haemostasis.*

It is a condition of registration that the first five batches of Artiss fibrin sealant VH S/D 4 IU (frozen) (AUST R 163515) imported into Australia are not released for sale until: (1) samples of each batch have been tested and approved by OLSS, and (2) the manufacturer's release data have been evaluated and approved by OLSS. These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The sponsor may also be required to provide evidence of satisfactory shipping conditions to Australia for every batch imported. These conditions remain in place until the sponsor is notified officially in writing of any change.

### **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

# ARTISS

## NAME OF THE MEDICINE

### ARTISS

Two-Component Fibrin Sealant, Deep-Frozen, Vapour Heated (VH) and Solvent Detergent (S/D) treated.

## DESCRIPTION

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.

### Table 1: Composition of the Active Ingredients of ARTISS:

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

Active ingredients	Quantity
As total protein	96 – 125 mg
Thereof Fibrinogen (Clottable Protein)	72 – 110 mg
Factor XIII (human)	1.2 – 10 IU
Aprotinin, synthetic (Fibrinolysis Inhibitor)	3000 KIU <sup>1</sup>
Excipients (see below)	

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

<sup>1</sup> KIU = Kallidinogenase Inactivator Unit

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

Active ingredients	Quantity
Thrombin (human)	4 IU <sup>2</sup>
Calcium Chloride (2 H <sub>2</sub> O)	40 µmol
Excipients (see below)	

The 2 components of ARTISS are colourless to pale yellow, opalescent when frozen and clear to slightly turbid solutions once defrosted.

**Table 2: Composition of the Excipients of ARTISS:**

**(1) Sealer Protein Solution:** 1 mL of the solution contains, Human Albumin (10-20 mg), Histidine (10-25 mg), Sodium Citrate (4.8-9.7 mg), Polysorbate 80 (0.6–1.9 mg), Nicotinamide (3–9 mg), Water for injection q.s. to 1 mL.

**(2) Thrombin Solution:** 1 mL of the solution contains, Human Albumin (45–55 mg), Sodium Chloride (3.5–5.5 mg) and Water for injection q.s to 1 mL.

**Chemical structures**

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 $\beta$ ,  $\gamma$ )<sub>2</sub> and has a molecular weight (MW) of about 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  $\gamma$ -chain 411 amino acids (MW about 47 000). Thus, the entire human fibrinogen contains 2964 amino acids.

Thrombin (human origin) is a glycosylated protein, consisting of two polypeptide subunits A and B, covalently linked by one -S-S- bond. The molecular weight is about 33 800. The human thrombin subunit A chain is made of 36 amino acids, whilst the B chain contains 259 amino acids.

<sup>2</sup> Thrombin activity is calculated using the current WHO International Standard for thrombin.

Factor XIII (human origin), also called blood-coagulation factor XIII, is a tetramer composed of two a-chains and two b-chains (each of a molecular weight of about 80 000) which are non-covalently associated.

Aprotinin (synthetic origin) is a protease inhibitor, a polypeptide consisting of one chain of 58 amino acids with a molecular weight of 6511.5, also stabilized by -S-S- bonds.

## PHARMACOLOGY

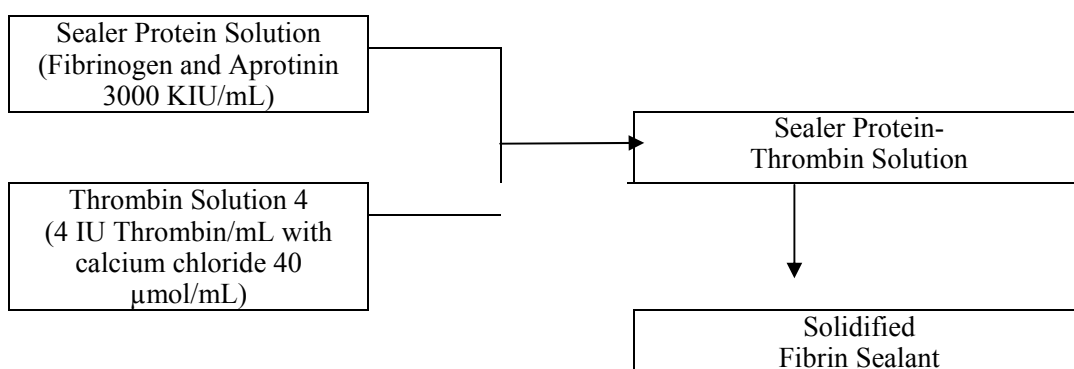
Pharmacotherapeutic group: local hemostatics, ATC code: B02BC; tissue adhesives, ATC code: V03 A K

### Pharmacodynamics

ARTISS contains two components, Sealer Protein Solution and Thrombin Solution. The Sealer Protein Solution contains fibrinogen as the main active ingredient, and 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 polymerises 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 4 IU thrombin has demonstrated adhesion of autologous split skin grafts to surgically prepared wound beds in a pig model.

### **Pharmacokinetics**

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

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

## **CLINICAL TRIALS**

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 report 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 at both test sites on Day 28. The median age of subjects was 31 years, range 1-62 years. 14% were  $\leq 6$  years of age and 15% 7-18 years of age. 66% of the subjects were male. Similar areas were treated at the two sites:  $1.7 \pm 0.8\%$  body surface area at ARTISS sites and  $1.7 \pm 0.7\%$  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 Table 3 below:

**Table 3: Test Sites with Complete Wound Closure on Day 28**

	<b>ARTISS</b>	<b>Staples (control)</b>	<b>Difference [95% CI]</b>	<b>Difference [97.5% CI]<sup>1</sup></b>
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%, -]

<sup>1</sup> 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 (Table 4).

**Table 4: Summary of Secondary Efficacy Endpoints – Categorical Variables / Intent-to-Treat**

	<b>ARTISS</b>	<b>Staples</b>	<b>Difference [95% CI]</b>
	[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%]

## INDICATIONS

Artiss is indicated to adhere autologous skin grafts in burn patients. ARTISS is not indicated for haemostasis.

## CONTRAINDICATIONS

ARTISS is contraindicated in the case of hypersensitivity to the active substances or to any of the excipients.

ARTISS is contraindicated for intravascular application. Intravascular application may result in life-threatening thromboembolic events.

Soft tissue injection of ARTISS carries the risk of local tissue damage.

## PRECAUTIONS

ARTISS alone is not indicated for the treatment of massive and brisk arterial or venous bleeding. As with any protein-containing product, allergic type hypersensitivity reactions are possible. Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of fibrin sealant. In specific cases, these reactions have progressed to severe anaphylaxis.

Such reactions may especially be seen if ARTISS is applied repeatedly over time or in the same setting, or if systemic aprotinin has been administered previously. Even if the first treatment was well tolerated, a subsequent administration of ARTISS or systemic aprotinin may not exclude the occurrence of an allergic reaction. Such reactions may also occur in patients receiving ARTISS for the first time.

Discontinue administration of ARTISS in the event of anaphylactic or hypersensitivity reactions. Remove the already applied, polymerized product from the surgical site. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

Sealer protein concentrate and thrombin are made from human plasma. 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 standard measures taken (including double virus inactivation by vapour heat treatment and solvent detergent treatment) are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

These standard 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.)

### **Effects on Fertility**

Studies of the effect of TISSEEL on fertility have not been performed.

### **Use in 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.

### **Use in lactation**

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.

### **Paediatric use**

Efficacy and safety in the paediatric population was not different from the adult population.

### **Use in the elderly**

ARTISS has not been administered to >65 year old subjects in clinical trials.

### **Carcinogenicity**

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

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### Genotoxicity

Studies of genotoxic potential of ARTISS have not been performed.

### Interactions with other medicines

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.

## ADVERSE EFFECTS

### Adverse Reactions from Clinical Trials

In a phase 3, multi-centered, 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).

**Table 4: Clinical Trial Adverse Reactions**

System Organ Class (SOC)	Preferred MedDRA Term	Frequency	Frequency Ratio
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dermal cyst	Uncommon	1/138
	Pruritus	Common	2/138
INJURY POISONING AND PROCEDURAL COMPLICATIONS	Skin graft failure	Common	5/138

Legend: ADR frequency is based upon the following scale: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ).

**Post marketing Adverse Reactions**

There are limited post-marketing data available for ARTISS.

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, 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

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

There is a report of fatal air embolism associated with the use of another fibrin sealant 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.

## **DOSAGE AND ADMINISTRATION**

ARTISS should be administered topically. Do not inject. ARTISS may be denatured by antiseptics (see Interactions with other medicines).

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.

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

After the graft or flap 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.

### Cannula

The cannulas included with the DUPLOJECT Preparation and Application System or DUO 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 (2 mL/100 cm<sup>2</sup>) to avoid formation of excessive granulation tissue and interference with wound healing.

### 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:

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Approximate area requiring tissue adherence	Required package size of ARTISS
100 cm <sup>2</sup>	2 mL
200 cm <sup>2</sup>	4 mL
500 cm <sup>2</sup>	10 mL

This recommended dose applies to all age groups.

#### Method of Preparation of ARTISS Preloaded Syringe (Frozen)

- Unopened pouches, thawed at room temperature, may be stored for up to 7 days at controlled room temperature (not exceeding + 25°C). If not used within 7 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. (The temperature of 37°C must, however, not be exceeded.)
- 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)
2 mL	5 minutes
4 mL	5 minutes
10 mL	12 minutes

Option 2 – Thawing off the sterile field

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)
2 mL	30 minutes
4 mL	40 minutes
10 mL	80 minutes

Option 3 – Thawing off the sterile field

incubator (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:

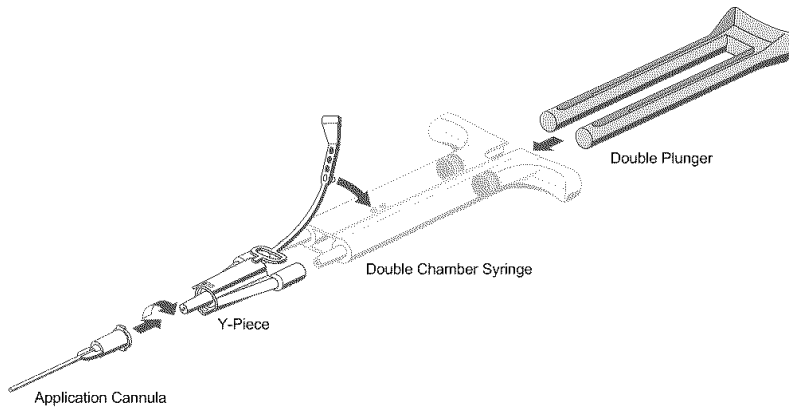
Pack Size	Thawing/Warming Times 33°C to 37°C Incubator (In Pouches)
2 mL	40 minutes
4 mL	85 minutes
10 mL	105 minutes

**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 ADVERSE EFFECTS). 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.

When applying ARTISS using a spray device, keep within the pressure recommended by the spray device manufacturer. In the absence of a specific recommendation, avoid using pressure above 140-170 kPa (20-25 psi). Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation, avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying ARTISS, changes in blood pressure, pulse oxygen saturation and end tidal CO<sub>2</sub> should be monitored because of the possibility of air or gas embolism.

## OVERDOSAGE

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. In the event of overdosage, please contact the Poison Information Centre at Phone Number: 131126.

## PRESENTATION AND STORAGE CONDITIONS

### 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 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)

ARTISS is available in the following pack sizes:

- ARTISS, 2.0 mL (containing 1.0 mL of Sealer Protein Solution and 1.0 mL of Thrombin Solution)
- ARTISS, 4.0 mL (containing 2.0 mL of Sealer Protein Solution and 2.0 mL of Thrombin Solution)
- ARTISS, 10.0 mL (containing 5.0 mL of Sealer Protein Solution and 5.0 mL of Thrombin Solution)

(See Table 3 below for formulation details)

### Incompatibilities

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

### Shelf Life

Deep frozen ARTISS has a shelf life of two years at temperatures < -20°C. The expiry date is stated on the final container and the package.

Unopened pouches, thawed at room temperature, may be stored for up to 7 days at controlled room temperature (not exceeding + 25°C). If not used within 7 days after thawing, ARTISS must be discarded. After thawing, the solutions must not be refrigerated or refrozen!

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.

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.

**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.

Once thawed, do not refreeze or refrigerate.

**Keep out of reach and sight of children.**

**For single use only. Do not re-sterilise!**

**Set of Devices**

Each pack ARTISS contains a double-sterile set of devices (DUO SET) 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 DOSAGE AND ADMINISTRATION –section Operating Instructions.

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

**POISON SCHEDULE OF THE MEDICINE**

Unscheduled

**NAME AND ADDRESS OF THE SPONSOR**

Baxter Healthcare Pty Ltd  
1 Baxter Drive  
Old Toongabbie  
NSW 2146

**DATE OF APPROVAL**

03 August 2010

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

**[www.tga.gov.au](http://www.tga.gov.au)**