Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fibrin adhesive/sealant

Proprietary Product Name: Artiss

Sponsor: Baxter Healthcare Pty Ltd

February 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
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- 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 <http://www.tga.gov.au>.

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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I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications
Decision:	Approved
Date of decision:	21 December 2011

Active ingredient:	Fibrin adhesive/sealant
Product name:	Artiss
Sponsor's name and address:	Baxter Healthcare Pty Ltd 1 Baxter Drive Toongabbie NSW 2146
Dose form:	Two deep frozen solutions in pre-filled syringes
Strengths:	1 mL, 2 mL and 5 mL of each solution
Containers:	Both Sealer Protein Solution and Thrombin Solution are contained in two separate chambers of a single use double chamber syringe made of polypropylene.
Pack sizes:	2 mL, 4 mL and 10 mL
Approved therapeutic use:	To adhere autologous skin grafts in burns patients. To adhere tissue flaps during facial rhytidectomy surgery (facelift). Artiss is not indicated for haemostasis.
Route of administration:	Topical
Dosage:	Individualised – see Product Information
ARTG number:	163515

Product background

Artiss is a fibrin adhesive/sealant product. It is a mixture of human plasma derived coagulation factors which when mixed together result in the formation of a solid fibrin clot. It was initially registered in 2010 following consideration by the Advisory Committee on Prescription Medicines (ACPM) at its June 2010 meeting. It is currently registered for the adherence of autologous skin grafts in burns patients.[1]

The product is presented as two separate solutions which are mixed at the site of application by means of a double syringe device. The syringe can be attached to a spray device to enable application of the mixture to large surface areas. The active ingredients in the currently registered formulation are as follows:

1. "Sealer Protein Solution"
   - Fibrinogen (human) 72 – 110 mg per mL Coagulation factor
   - Factor XIII (human) 1.2 – 10 IU per mL Coagulation factor
   - Aprotinin (synthetic) 3000 KIU per mL Fibrinolysis inhibitor
2. "Thrombin Solution"
   - Thrombin (human) 4 IU per mL Coagulation factor

[1] TGA, AusPAR for Fibrin sealant (Artiss), October 2010. Available at: <http://www.tga.gov.au/pdf/auspar/auspar-artiss.pdf>

– Calcium chloride 40 mmol per mL Clotting activator

The sponsor also markets another fibrin sealant/adhesive product under the tradename 'Tisseel VH/SD'. This product contains a higher concentration of thrombin and is currently approved as haemostatic agent and as an adhesive or sealant in various settings.

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 haemostasis and sealing of tissues. 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 re-bleeding or detachment of sealed tissues.

Rapid haemostasis and sealing can be achieved with high amounts of thrombin (Tisseel VH S/D 500 IU thrombin in Thrombin Solution) resulting in virtually immediate clot formation. For this reason thrombin concentrations of 500 IU/mL are usually used for surgical procedures where haemostasis and sealing have to be as fast as possible, as per the currently approved indication for Tisseel VH S/D. However, in situations when time for additional handling is needed after applying the sealant, low thrombin concentrations (4 IU/mL) are of considerable advantage. Due to the longer clotting time, sealants containing low amounts of thrombin are used as biological tissue glues for procedures such as skin grafting (as per the currently approved indication for Artiss) or to adhere skin flaps and grafts during facial plastic and reconstructive surgeries (as per the proposed new indication).

This AusPAR describes the evaluation of a submission by Baxter Healthcare Pty Ltd (the sponsor) to extend the indications for Artiss from:

Artiss is indicated to adhere autologous skin grafts in burns patients. Artiss is not indicated for haemostasis, to include:

To adhere skin flaps and grafts during facial plastic and reconstructive surgery.

The proposed dose for the new indication is the same as that currently approved for skin grafts in burns patients.

Regulatory status

The product received initial ARTG Registration in October 2010.

Artiss was approved on 16 February 2011 in Austria as the European Union (EU) Reference Member State. The national implementation phase is in progress. The EU indication is:

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

Artiss was approved in Canada on 18 August 2010 with the indication:

Artiss (Fibrin Sealant (Human) is indicated for the fixation (glue) of autologous skin grafts and skin flaps and adjunct to hemostasis on subcutaneous tissue surfaces to treat burns in adult and pediatric patients.

Artiss was approved in the US on 29 August 2010 for the indications:

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

- *Artiss is indicated to adhere tissue flaps during facial rhytidectomy surgery (facelift).*
- *Artiss is not indicated as an adjunct to hemostasis.*

Artiss was approved in Switzerland on 9 December 2009 for the burn indication only and is under review in New Zealand for the same indication.

Product Information

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

II. Quality findings

Quality summary and conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Nonclinical summary and conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

Two clinical studies were provided in support of the application.

Study 550703 was a Phase II, prospective, randomized, controlled, evaluator blinded, multicentre study comparing the adjuvant use of Artiss to Standard of Care (SoC) in adhering tissue in subjects undergoing rhytidectomy (facelift) surgery.

Study 550901 was a Phase III, prospective, randomized, controlled, subject blinded, multicentre study comparing the safety and efficacy of adjuvant Artiss versus SoC in adhering tissue in subjects undergoing rhytidectomy.

Both studies utilised a split face approach, where a single subject acted as his or her own control. A major function of Study 550703 was to identify suitable objective clinical endpoints, which were then applied in Study 550901. For this application, Study 550901 was the pivotal study.

Pharmacokinetics/pharmacodynamics

No new information was received on pharmacokinetics as part of this application. This was appropriate given the nature of the application and the product.

No new information was provided on pharmacodynamics. Artiss is a topical fibrin sealant applied locally to treatment sites to form an elastic fibrin clot, and has been well characterised in the previous application.

Efficacy

Main (pivotal) study - Study 550901

Objectives

The purpose of this study was to compare the safety and efficacy of adjuvant Artiss versus SoC in adhering tissues in subjects undergoing rhytidectomy. The primary objective was to evaluate the effect of Artiss on the improvement of flap adherence in subjects undergoing rhytidectomy, as indicated by a reduction in drainage volume. Secondary objectives included analysis of haematoma and seroma, comparison of oedema, changes in skin sensitivity, assessment of subject side of face preference, and assessment of safety profile through recording of adverse events.

Study participants

A total of 75 subjects were enrolled and were healthy adults planned for rhytidectomy. Inclusion/exclusion criteria are shown in Table 1.

Table 1: Inclusion/exclusion criteria

Inclusion Criteria

- Male or female subject is 18 to 75 years of age at the time of screening.
- Subject is planned for facial rhytidectomy.
- Subject has read, understood and signed the written informed consent.
- Subject is healthy, as determined by the investigator using standard pre-operative assessments to include laboratory tests and electrocardiograms.
- Subject is of childbearing potential, presents with a negative serum pregnancy test, and agrees to employ adequate birth control measures for the duration of the study.
- Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

- Subject is indicated for an abbreviated or modified face-lift procedure such as deep plane procedures, minimal undermining procedures, thread lifts, and minimal access cranial suspension.
- Subject is indicated for concurrent facial surgeries during the operation (eg forehead plasty, blepharoplasty, rhinoplasty, buccal fat removal, any filler injections including fat injections, lip augmentation, skin resurfacing procedures etc.).
- Subject is indicated for additional procedures to the body during the same operation (eg liposuction, mastoplasty etc.).
- Subject has undergone a prior rhytidectomy surgery.
- Subject is an active smoker, as assessed by the investigator.
- Subject has a known (documented) bleeding or coagulation disorder.
- Subject is being treated with anti-coagulants or with Aspirin (that was not discontinued 7 days prior to surgery).
- Subject has a vascular disorder, cardiovascular disease, and/or uncontrolled hypertension.
- Subject has diabetes mellitus with glycosylated hemoglobin (HbA1c) > 7.
- Subject is receiving active treatment for a malignancy.
- Subject has a connective tissue disorder.
- Subject has an active or chronic skin disorder.
- Subject has history of Bell's palsy.
- Subject has a documented history of pathologically or pharmacologically induced immune deficiency.
- Subject has received chronic treatment with immunosuppressive drugs, systemic corticosteroids, or other chronic treatments within 30 days prior to the surgery.
- Subject has a known sensitivity to components of FS VH S/D 4 s-apr.
- Subject has a known psychiatric disorder (eg, obsessive compulsive disorder, anxiety, eating disorders, etc.).
- Subject has documented healing complications following previous surgeries (eg, hypertrophic scarring).
- Subject is pregnant or lactating at the time of enrollment.
- Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.

Treatments

This was a split face study, where one side of the face was treated with Artiss as adjuvant to SoC and the other side was to receive SoC alone. Surgery was conducted by 7 different plastic surgeons and involved a full undermining of the skin and manipulation of the soft tissue. Adjuvant facial, nasal or ocular liposuctions were not to be performed, although liposuction of the neck/jowls was permitted. Postoperative follow up was planned for a period of 14 days. The study was conducted across 7 different geographical locations in the USA.

Outcomes/endpoints

The primary efficacy endpoint was the total drainage volume collected from each side of the face at 24 hours (h) (±4 h) post surgery. Secondary efficacy endpoints were the occurrence of haematoma and seroma on each side of the face, comparison of oedema between the 2 sides of the face, changes in skin sensitivity from baseline, subject preference, subject assessment of numbness and additional humanistic outcomes. The primary safety endpoint was the incidence of adverse events (AEs) related to the product throughout the study period. Skin sensation was assessed on Day 0, 3, 7 and 14 using Semmes-Weinstein Monofilament administered by the investigator. The test was administered in the middle of the imaginary line running between the tragus and the mouth commissure. Numbness was assessed by the investigator asking the subject to assess their numbness on a scale of 1-10 at each postoperative visit.

Statistical considerations

Sample size calculations were based on drainage volume data collected in study 550703. In that study, mean difference in drainage was 15.5±22.95 mL. Assuming a 10% decrease in mean difference in drainage volumes between the 2 sides of the face and with a 50% increase in the observed standard deviation of the paired differences, a sample size of 75 was required to obtain 91% power in a 2-sided paired t-test with a non-parametric adjustment, alpha=0.05. For the secondary endpoint of haematoma/seroma occurrence, a sample size of 75 yields 87% power in a McNemar test with an assumed total discordant proportion of 0.23 and with a difference in discordant proportions between the 2 sides of the face of 0.17%.

The side of the face to be operated on first and the side of the face to receive Artiss were determined by a predefined randomisation scheme.

Subjects were blinded as to which side of the face had received adjuvant Artiss. The surgeon/investigator assessing the endpoints of drainage volume, haematoma/seroma and oedema was not blinded and this was probably appropriate given the requirement for routine postoperative care to be provided by the surgeon.

The primary efficacy endpoint analysis was carried out on the “full analysis” (FA) and “per protocol” (PP) sets. The PP analysis set was a subset of the FA set and included those subjects who met all inclusion/exclusion criteria, were randomised and treated according to the protocol and adhered to study procedures with no major protocol deviations. Total volume of drainage at 24 h (±4 h) post-surgery on each side of the face was to be summarised with descriptive statistics. To assess the difference in drainage volume between the 2 sides of the face, a 2-sided paired t-test was conducted at an alpha level of 5%. The primary safety endpoint was the incidence of AEs related to Artiss throughout the study period. Assessment of other efficacy endpoints primarily involved assessment of proportions of clinical endpoints between the two sides of the face, with comparison utilising a 2-sided McNemars test of paired proportions at an alpha level of 5%. A 95% confidence interval (CI) around the difference in the paired proportions was computed.

Results

Participant flow

A total of 79 patients were enrolled and 75 (94.9%) completed. Two patients failed screening and two other patients did not complete the study.

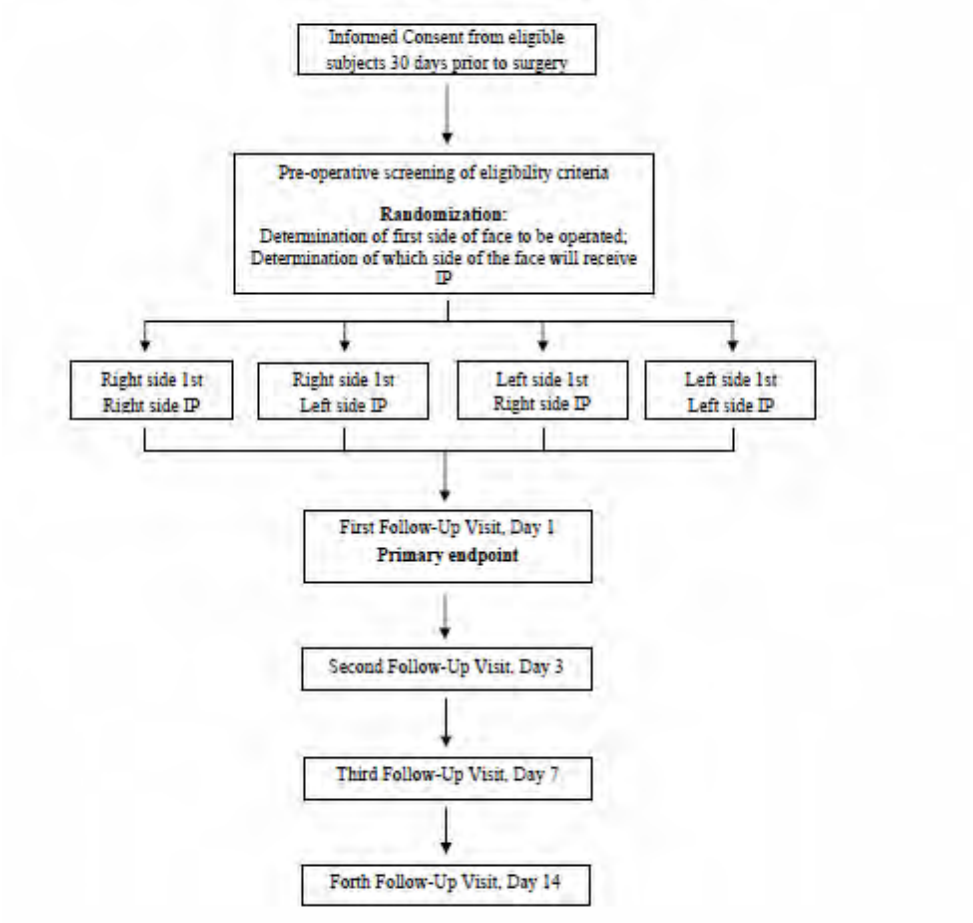
Recruitment

Recruitment was conducted from subjects who had actively approached the investigator for consultation regarding facial rhytidectomy surgery.

Conduct of the study

The study design is shown in Figure 1.

Figure 1: Study flow chart



Baseline data

Baseline data on demographics, medical history, indications for surgery, physical, head and neck examination, concomitant medicines and pregnancy tests were collected but not reported.

Numbers analysed

A total of 75 subjects were analysed, with 69 subjects available for the PP set, 75 subjects available for the FA set and 75 subjects for the safety set.

Outcomes and estimation

Results of this study are shown in Tables 2, 3 and 4. A statistically significant difference in drainage volumes was observed, favouring the side of the face treated with adjuvant Artiss. For the FA dataset, a mean±SD (standard deviation) volume of 7.7±7.4 mL drained after 24 h for the Artiss treated side, compared to a mean volume of 20.0±11.3 mL at the SoC side of the face ($p<0.0001$) (Table 2). The mean±SD difference in 24 h postoperative drainage between the subjects 2 sides of the face was 12.3±11.4 mL in favour of the Artiss treated side. While there was a noticeably larger difference in drainage volumes treated at site 3, the difference overall remained statistically significant if this site was excluded.

For haematoma/seroma occurrence, 7 events in a total of 5 subjects occurred on the Artiss side, compared to 8 events in a total of 8 subjects for the SoC side (Table 3). There was no statistically significant difference. For the assessment of oedema, the differences in the proportions of subjects deemed to have less oedema on the Artiss side compared to the

SoC side were statistically significant at each study visit the assessment was performed (Table 4). However the investigators could not be blinded to treatment in this study. There were no statistically significant differences noted for skin sensitivity or numbness endpoints. For the subject assessment of preference for one side of the face over the other, the majority of subjects stated a preference for the Artiss treated side of the face over the SoC treated side of the face at each postoperative day. For the FA set at Day 1, 63% of subjects preferred the side of the face treated with Artiss, compared to 21% of subjects that preferred the side of the face with SoC. For all endpoints, results were consistent between FA and PP analyses.

Table 2: Comparison of drainage volume (mL) at 24 h postoperative (FAS)

Statistic[a]	Standard of Care	FS VH S/D 4 s-apr	Difference	p-value[a]
Mean	20.0	7.7	12.3	<.0001
Median	20.0	8.0	11.0	
Inter-quartile Range	18.0	10.0	15.0	
Standard Deviation	11.3	7.4	11.4	
Minimum	0	0	-17	
Maximum	50	39	40	
N	75	75	75	

[a] p-value from two-sided paired t-test with alpha = 5%

Table 3: Number (proportion) of subjects with haematoma/seroma anytime during the study

Analysis Set [a]	Number (Proportion) of Subjects with Hematoma/Seroma on FS VH S/D 4 s-apr Side	Number (Proportion) of Subjects with Hematoma/Seroma on Standard of Care Side	Number (Proportion) of Subjects with Hematoma/Seroma on Both Sides	Number (Proportion) of Subjects with No Hematoma/Seroma on Either Side
Full Analysis Set (N=75)	2 (0.027)	5 (0.067)	3 (0.040)	65 (0.867)
Per Protocol Set (N=69)	2 (0.029)	5 (0.072)	3 (0.043)	59 (0.855)

[a] (N=) indicates the number of subjects in analysis set.

Table 4: Summary of outcomes of the investigators' visual comparisons of oedema on postoperative Days 1, 3, 7, 14 (FAS)

Study Day[a]	Number (Proportion) of Subjects with Less Edema with FS VH S/D 4 s-apr	Number (Proportion) of Subjects with Less Edema with Standard of Care	Number (Proportion) of Subjects with No Difference in Edema
DAY 1 (N=75)	40 (0.53)	12 (0.16)	23 (0.31)
DAY 3 (N=75)	41 (0.55)	12 (0.16)	22 (0.29)
DAY 7 (N=73)	41 (0.56)	15 (0.21)	17 (0.23)
DAY 14 (N=74)	27 (0.36)	13 (0.18)	34 (0.46)

[a] (N=) indicates the number of subjects providing data.

Supportive study 550703

Study 550703 was a Phase II, prospective, randomized, controlled, evaluator blinded, multicentre study comparing the adjuvant use of Artiss to Standard of Care (SoC) in adhering tissue in subjects undergoing rhytidectomy (facelift) surgery. The purpose of the study was to explore endpoints and evaluate the efficacy and safety of Artiss in improving

tissue plane adherence and local haemostasis in subjects undergoing rhytidectomy. The primary efficacy objective was to evaluate the efficacy and safety of Artiss in reducing early postoperative ecchymosis (bruising on Day 3). Secondary objectives were to evaluate ecchymosis, oedema, drainage volume, haematoma, seroma, pain, numbness and facial sensation perception. This was a split face rhytidectomy study design where one side of the face was treated with Artiss and SoC, and the other side received SoC only. Allocation of the side of the face that was to receive Artiss was to be determined by a pre-defined randomization scheme. Subjects were followed up for 14 days postoperatively. Subjects were healthy adults and a total of 45 subjects were enrolled. Surgery was conducted by 6 different plastic surgeons and involved a full undermining of the skin and manipulation of the soft tissue. Adjuvant facial, nasal or ocular liposuctions were not to be performed.

The primary efficacy endpoint was the visual comparison of ecchymosis at Day 3 between the Artiss adjuvant treated side of the face and the SoC treated side of the face, as assessed by 5 independent blinded reviewers using standard digital photographs. Secondary efficacy endpoints included visual comparison of ecchymosis at Days 1, 5, 7, 10 and 14, grade of ecchymosis, grade of oedema, resolution of bruising and resolution of swelling, total volume of drainage at 24 h, occurrence of haematoma/seroma, 2 point discrimination test, subjective assessment of pain and numbness, subject side of face preference and incidence of adverse events. In terms of statistical analysis, the proportion of subjects whose side of the face treated with Artiss was evaluated as having less ecchymosis than the side of the face that received SoC was to be compared to the proportion of subjects whose side of the face that received SoC was evaluated as having less ecchymosis than the side of the face treated with Artiss. These proportions were compared in a 2-sided McNemar's test of paired proportions at an alpha level of 5%. A sample size of 40 was selected as appropriate, assuming that 25% of the subjects were to have discordant assessments for the 2 treatments and also assuming that Artiss was to result in at least 22% fewer instances of ecchymosis than the SoC control. This sample size would insure a power greater than 80% using the exact McNemar test at a 2-sided 5% level.

Results of this study are shown in Tables 5 and 6. Results for the PP dataset revealed that 18% of subjects had less ecchymosis on the side of the face treated with Artiss, 43% had less ecchymosis on the side of the face treated with SoC alone and 39% of subjects had equal levels of ecchymosis on both sides of the face (Table 5). No statistically significant difference was observed at Day 3. This was also the case for the majority of secondary objectives, with the exception of drainage volumes at 24 h and occurrence of haematoma/seroma. The mean drainage volume at 24 h for the Artiss side of the face was < 12 mL, compared to > 24 mL for the SoC side (Table 6). This was statistically significant for both the PP and ITT analysis (p=0.0010 and p<0.0001). No haematoma or seroma was noted on the Artiss side of the face, compared to 18% and 20% of SoC receiving sides in the PP and ITT analyses. This was also statistically significant (p=0.014 and p=0.003).

Table 5: Summary of outcomes of the visual comparisons of ecchymosis between two sides of face as assessed by a majority of blinded reviewers on Day 3 – primary endpoint

Analysis Set[a]	Number(Proportion) of Subjects with Less Ecchymosis with FS VH S/D 4	Number(Proportion) of Subjects with Less Ecchymosis with Standard of Care	Number(Proportion) of Subjects with Equal Ecchymosis	Number(Proportion) of Subjects with No Ecchymosis on Either Side
Per Protocol (N=28)	5 (0.18)	12 (0.43)	11 (0.39)	0 (0.00)
Intent to Treat (N=37)	7 (0.19)	17 (0.46)	13 (0.35)	0 (0.00)

[a] (N=) indicates the number of subjects with an outcome assigned by majority of reviewers (3 or more).

Table 6: Comparison of drainage volume (mL) at 24 h postoperative (PPS)

Table 14.2-25
Comparison of Drainage Volume (mL) at 24 Hours Postoperative / Per Protocol

Statistic*	Standard of Care	FS VH S/D 4	p-value*
Mean	24.3	11.4	0.0010
Median	16.0	5.0	
Inter-quartile Range	22.0	22.0	
Standard Deviation	22.9	14.8	
Minimum	0.0	0.0	
Maximum	100.0	50.0	
N	33	33	

* p-value from two-sided paired t-test with alpha = 5%.

Evaluator's overall conclusions on clinical efficacy

Information on clinical efficacy was available for 2 studies, study 550703 and study 550901. Study 550703 was a Phase II, prospective, randomized, controlled, evaluator blinded, multicentre study comparing the adjuvant use of Artiss to Standard of Care (SoC) in adhering tissue in subjects undergoing rhytidectomy (facelift) surgery. Study 550901 was a Phase III, prospective, randomized, controlled, subject blinded, multicentre study comparing the safety and efficacy of adjuvant Artiss versus SoC in adhering tissue in subjects undergoing rhytidectomy. Both studies utilised a split face approach, where a single subject acted as his or her own control. A major function of study 550703 was to identify suitable objective clinical endpoints, which were then applied in study 550901. Both studies were appropriately designed and powered.

With regard to results, study 550703 did not reveal any statistically significant differences for the primary efficacy endpoint (ecchymosis) but did reveal a statistically significant difference for drainage volumes at 24 h and occurrence of haematoma/seroma. For the Phase III study, there was a statistically significant difference in drainage volumes, favouring the side of the face treated with adjuvant Artiss. For the FA dataset, a mean±SD volume of 7.7±7.4 mL drained after 24 h for the Artiss treated side, compared to a mean volume of 20.0±11.3 mL at the SoC side of the face ($p<0.0001$). The mean±SD difference in 24 h postoperative drainage between the subjects 2 sides of the face was 12.3±11.4 mL in favour of the Artiss treated side. There was no statistically significant difference for haematoma/seroma.

Guidance on industrially manufactured fibrin sealant products is provided by the TGA-adopted EU guideline.[2] This document requires that efficacy has to be assessed in studies with objective clinical endpoints and that clinical studies need to be designed in which the appropriate endpoint is assessed for each therapeutic indication proposed. Such studies also need to be controlled. No specific endpoints are identified in the document with regard to rhytidectomy. In this submission, the sponsor has provided a justification to utilise drainage volume at 24 h as the primary efficacy endpoint, with the occurrence of haematoma/seroma as a secondary efficacy endpoint. This justification is supported by the results from the Phase II study, as well as current knowledge of healing processes. A number of supporting articles were provided which largely pertained to the possible role of fibrin sealants in wound healing. In the pivotal study, there was a statistically significant difference between the Artiss treated side and the SoC treated side, which would suggest

[2] 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>.

that the use of Artiss did result in a reduction in drainage volume at 24 h. However the implications of this with regard to long term outcomes post rhytidectomy are unknown, and further follow up may be of benefit. Both studies were performed in the context of rhytidectomy, although many of the techniques required for this procedure would be similar to other facial/plastic reconstructive surgery.

Safety

Introduction

Information on clinical safety was provided from the 2 clinical studies, study 550703 and study 550901. Both studies were controlled, using a split face approach. In addition, limited information on safety was available from postmarketing surveillance.

Patient exposure

A total of 120 subjects received Artiss, 45 in the Phase II study and 75 in the Phase III study. All subjects were candidates for rhytidectomy (facelift) surgery and were otherwise well. A summary of volumes received is shown in Table 7.

Table 7: Summary of volume of Artiss applied

Statistic	550703	550901	Overall
Number of Subjects	45	75	120
Mean (mL)	2.3	2.6	2.5
Median (mL)	2.0	2.2	2.1
Inter-Quartile Range (mL)	1.5	2.5	2.1
Standard Deviation (mL)	0.9	1.2	1.1
Minimum (mL)	0.8	0.6	0.6
Maximum (mL)	4.0	4.0	4.0

Adverse events

Adverse events were assessed in all subjects, up to 14 days postoperatively. In addition, some adverse events were assessed as part of the efficacy endpoints, including haematoma/seroma, ecchymosis and oedema. Integrated summaries are shown as an overview (Table 8).

Table 8: Overview of all adverse events that occurred during or after surgery

Serious	Severity	Relationship	Number of AEs	Number of Subjects[a]	Percent of Subjects (%)[b]
Serious	Mild	Unrelated	0	0	0.0
		Related	0	0	0.0
		Total	0	0	0.0
	Moderate	Unrelated	2	2	1.7
		Related	1	1	0.8
		Total	3	3	2.5
	Severe	Unrelated	0	0	0.0
		Related	0	0	0.0
		Total	0	0	0.0
	Total	Unrelated	2	2	1.7
		Related	1	1	0.8
		Total	3	3	2.5
Non-Serious	Mild	Unrelated	47	33	27.5
		Related	2	2	1.7
		Total	49	34	28.3
	Moderate	Unrelated	4	4	3.3
		Related	0	0	0.0
		Total	4	4	3.3
	Severe	Unrelated	0	0	0.0
		Related	0	0	0.0
		Total	0	0	0.0
	Total	Unrelated	51	37	30.8
		Related	2	2	1.7
		Total	53	38	31.7
Total	Total	Unrelated	53	38	31.7
		Related	3	3	2.5
		Total	56	39	32.5

a. Total number of subjects may not add up, due to subjects having several AEs.
b. Percent is based on total number of subjects in safety analysis data: 120.

In study 550901, there was a total of 11 facial AEs in 6 subjects occurring on the Artiss treated side, compared to 12 facial AEs in 11 subjects occurring on the SoC side. There were 6 facial AEs in 6 subjects occurring across both sides of the face and a total of 8 non-facial AEs in 6 subjects. Of the AEs in this study, two were classified as serious, in one subject a wound abscess with methicillin resistant *Staphylococcus aureus* (MRSA) on the Artiss treated side and one subject with dehydration. The wound abscess was felt to be

related to the Artiss, although this was not discussed at length in the study report. Results for adverse events occurring on the face are shown in Table 9.

Table 9: Adverse events occurring on the face - study 550901

	Artiss side	SoC side	Both sides
Patients with facial adverse event (AE)	6	11	6
Total No of facial AEs	11	12	6
No of adverse events			
Seroma	6	4	0
Haematoma	1	4	0
Pain	1	0	2
Swelling	1	0	0
Cellulitis	1	0	0
Wound abscess	1	0	0
Oral herpes	0	1	0
Contusion	0	1	0
Corneal abrasion	0	1	0
Wound dehiscence	0	1	0
Tongue abscess	0	0	1
Thermal burn	0	0	1
Paraesthesiae	0	0	1
Rash	0	0	1

In study 550703, a total of 19 adverse events (AEs) occurred in 17 subjects during the study. Of these, one was considered a serious adverse event (SAE), an incidence of basal cell carcinoma (BCC) and occurred on the SoC side of the face. Of the 19 AEs, 16 AEs in 14 subjects were categorised as locally occurring and 3 AEs in 3 subjects were categorised as systemic. Of the local AEs, 1 AE occurred exclusively on the side treated with Artiss, and 12 AEs occurred exclusively on the SoC treated side. Three AEs occurred across both sides of the face. No AEs were considered to be related to the investigational product. Adverse events occurring on the face are summarised in Table 10.

Table 10: Adverse events occurring on the face – study 550703

	Artiss side	SoC side	Both sides
Patients with facial adverse event (AE)	1	12	3
Total No of facial AEs	1	12	3
No of adverse events			
Seroma	0	2	0
Haematoma	0	7	0
Wound dehiscence	1	0	0
Oedema	0	1	3
Epidermolysis	0	1	0
BCC	0	1	0

Serious adverse events and deaths

Serious adverse events are discussed above. There were no deaths reported in either clinical study.

Postmarketing experience

Some additional information was provided with regard to postmarketing experience with Artiss. This consisted of details of three adverse event reports, including one report of a spontaneous graft complication, one report of drug ineffective/wrong technique and one report of product gelling. No significant safety concerns were identified as a result of these reports.

Evaluator's overall conclusions on clinical safety

Information on clinical safety was provided from the 2 clinical studies, study 550703 and study 550901. Both studies were controlled, using a split face approach. In addition, limited information on safety was available from postmarketing surveillance.

No significant issues with regard to safety were identified. Incidence of adverse events was comparable between the SoC and Artiss treated sides of the face. There was one SAE (wound abscess with MRSA) that was felt to be related to Artiss, however a number of other factors may have contributed to this occurrence. No significant issues have been raised from postmarketing surveillance.

Current guidance on clinical safety is provided by the TGA-adopted EU guideline.[2] This document identifies relevant safety issues as viral safety, safety with regard to transmissible spongiform encephalopathy (TSE), immunogenicity and adverse events. The first three of these were not addressed in this application, as they had previously been covered in the original application for this product.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated. There were no questions regarding this application.

Clinical summary and conclusions

Clinical aspects

Clinical efficacy

Information on clinical efficacy was available for 2 studies, Study 550703 and Study 550901.

Study 550703 was a Phase II, prospective, randomized, controlled, evaluator blinded, multicentre study comparing the adjuvant use of Artiss to Standard of Care (SoC) in adhering tissue in subjects undergoing rhytidectomy (facelift) surgery.

Study 550901 was a Phase III, prospective, randomized, controlled, subject blinded, multicentre study comparing the safety and efficacy of adjuvant Artiss versus SoC in adhering tissue in subjects undergoing rhytidectomy.

Both studies utilised a split face approach, where a single subject acted as his or her own control. A major function of study 550703 was to identify suitable objective clinical endpoints, which were then applied in study 550901. The selection of the primary efficacy endpoint did appear to have a reasonable clinical basis. The pivotal study, study 550901, demonstrated a statistically difference in the primary efficacy endpoint, drainage volume at 24 h. The mean±SD difference in 24 h postoperative drainage between the subjects 2 sides of the face was 12.3±11.4 mL in favour of the Artiss treated side. Both studies were appropriately designed and powered.

Clinical safety

Patient exposure

A total of 120 subjects received Artiss, 45 in the Phase II study and 75 in the Phase III study.

Adverse events

Adverse events were assessed in all subjects, up to 14 days postoperatively. In addition, some adverse events were assessed as part of the efficacy endpoints, including haematoma/seroma, ecchymosis and oedema. Incidence of adverse events was comparable between the SoC and Artiss treated sides of the face. There was one SAE (wound abscess with MRSA) that was felt to be related to Artiss, however a number of other factors may have contributed to this occurrence. No significant issues have been raised from postmarketing surveillance.

There were no deaths reported during the clinical studies.

Benefit risk assessment

Benefits

Artiss is a two component fibrin sealant for topical use. Artiss was approved by the TGA in August 2010 with an approved indication to adhere autologous skin grafts in burns patients (not haemostasis). This application sought to add a new indication, to adhere skin flaps and grafts during facial plastic and reconstructive surgery. The pivotal study, study 550901, demonstrated a statistically difference in the primary efficacy endpoint, drainage

volume at 24 h. The mean±SD difference in 24 h postoperative drainage between the subjects 2 sides of the face was 12.3±11.4 mL in favour of the Artiss treated side. This appears to be a clinically significant outcome and may improve patient outcomes.

Risks

The selection of an appropriate objective efficacy endpoint is necessary to demonstrate efficacy for any proposed new indication. In this submission, the sponsor has provided a justification to utilise drainage volume at 24 h as the primary efficacy endpoint, with the occurrence of haematoma/seroma as a secondary efficacy endpoint. While this appears reasonable, follow up was limited to 14 days and the relationship to long term outcomes is unknown. Risk in terms of adverse events appears to be acceptable and unchanged from that identified in the original application and approval. The postmarketing surveillance does identify some issues in terms of physical application of the product and this may have training implications for the sponsor.

Balance

On balance, Artiss has a favourable benefit-risk profile.

Conclusions

The addition of a new indication for Artiss, to adhere skin flaps and grafts during facial plastic and reconstructive surgery, appears to have an acceptable benefit risk profile.

V. Pharmacovigilance findings

Risk management plan

Safety specification

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR). The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 11.

Table 11: Ongoing safety concerns for Artiss

Safety Concerns	
Important Identified Risks:	Allergic reactions
	Thromboembolic events due to intravascular application
	Lack of efficacy due to drug administration error
Important Potential Risks:	Risk of transmission of infective agents
	Granulation tissue formation due to application of excess product
	Risk of air embolism, tissue rupture, and gas entrapment with compression with the use of spray devices
	Interaction/Incompatibility with other medicinal products
Important Missing Information:	Preclinical studies regarding subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation

The OPR reviewer noted that the sponsor stated that the newly identified safety concerns since the last EU RMP was submitted are as follows:

- Air embolism, tissue rupture and gas entrapment with use of spray devices was identified as a class effect for fibrin sealants; and
- Lack of efficacy due to drug administration error.

Consequently the sponsor had added the important identified risk: 'Lack of efficacy due to drug administration error' and the important potential risk: 'Risk of air embolism, tissue rupture, and gas entrapment with compression with the use of spray devices' as ongoing safety concerns in the updated RMP. Furthermore the important missing information: 'Interaction/incompatibility with other medicinal products' has now been classified as an important potential risk.

The summary of the Ongoing Safety Concerns was considered acceptable. However, in regard to the specified important missing information, the sponsor appears to have included clinical 'Use in pregnancy' and 'Use in lactation' under the general heading: 'Preclinical studies'. It was suggested that these nonclinical and clinical aspects be clarified as separate ongoing safety concerns in the next version of the RMP.

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.[3] The OPR reviewer noted that the newly identified safety concerns would not appear to warrant additional pharmacovigilance activities, therefore this was acceptable.

Risk minimisation activities

The sponsor concluded that the identified and potential risks described in the RMP have processes in place to minimise risk by routine risk minimisation activities and do not require additional risk minimisation activities.[4] The OPR reviewer noted that the newly identified safety concerns would not appear to warrant additional risk minimisation activities, therefore this was acceptable.

Summary of recommendations

The OPR provided these recommendations to the Delegate:

- If this application is approved the following specific condition of registration should be applied: "The Risk Management Plan Version: 004, dated February 2011 (Australia Version: 001), must be implemented."
- In regard to the specified important missing information, the sponsor appears to have included clinical 'Use in pregnancy' and 'Use in lactation' under the general heading:

[3] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[4] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

'Preclinical studies'. It was suggested that these nonclinical and clinical aspects be clarified as separate ongoing safety concerns in the next version of the RMP.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator recommended approval of the application.

Efficacy

Evidence for efficacy comes from two randomised controlled trials conducted in patients undergoing facial rhytidectomy (facelift) procedures – a pivotal phase III study (550901) an earlier phase II study (550703). In both studies, patients served as their own controls, with one half of the face being treated with surgery according to the usual standard of care (SoC), and the other half treated with SoC plus Artiss. The dose of Artiss was 0.02 – 0.04 mL per cm^2, applied by spraying to the subcutaneous plane. This dose is consistent with the currently approved dose.

In rhytidectomy, after repositioning of the skin flap and removal of excess skin, sutures are used to close the skin flap at its edges. This can potentially leave a dead space beneath the flap, with the potential for haematoma and seroma formation. The proposed benefit of using a fibrin adhesive such as Artiss is to improve adherence of the skin flap to the subcutaneous tissues and eliminate such dead space.

Study 550901 enrolled 75 subjects. Investigators were not blinded to the side of the face which received Artiss. Prior to the end of surgery a surgical drain was placed on each side, in the lower part of the neck. The primary endpoint was the total volume of drainage fluid collected in the first 24 hours. This is presumably a surrogate marker of the extent of adherence of the flap and elimination of dead space.

Use of Artiss was associated with a significant reduction in the mean volume of drainage fluid (7.7 vs 20.0 mL; $p < 0.0001$).

A number of secondary endpoints were studied:

- There was no significant difference in the proportion of patients who developed haematoma or seroma (27% with Artiss vs 67% with SoC; $p = 0.257$);
- There was a significant difference in the proportion of patients who developed oedema at each visit post-surgery. However, the evaluator noted that the investigators who assessed this endpoint were not blinded to treatment allocation;
- There was no significant difference in the proportion of patients who developed skin sensitivity or numbness;

- At all postoperative visits, a significantly greater proportion of subjects expressed a preference for the Artiss treated side of the face. Importantly, subjects were blinded to treatment allocation.

Study 550703 enrolled 45 subjects. In this study, evaluation of the efficacy endpoints was conducted by examination of photographs by a panel of 5 blinded, independent reviewers. Subjects were also blinded to treatment allocation.

The primary endpoint was the proportion of patients with ecchymosis (bruising) on postoperative Day 3. Results indicated that 19% of subjects had less bruising on the Artiss treated side compared with 46% who had less bruising on the on the SoC side. The difference was not statistically significantly different (p = 0.064).

Results of secondary endpoints included the following:

- There was no significant difference in bruising on Days 5, 7, 10 and 14;
- There was a significant reduction in mean drainage volume at 24 hours (11.5 mL with Artiss vs 26.8 mL with SoC; p <0.0001);
- There was a reduction in the proportion of patients with haematoma or seroma (0% with Artiss vs 20% with SoC).

The sponsor performed an integrated analysis across both studies on the number of subjects who experience haematoma or seroma exclusively on one side of the face. The results, shown in Tables 12 and 13, suggested that use of Artiss results in a significantly lower proportion of patients developing seroma or haematoma.

Table 12: Summary of subjects with haematoma/seroma by side of face

Number(%) of Subjects with Hematoma/Seroma on ARTISS Side	Number(%) of Subjects with Hematoma/Seroma on Standard of Care Side	Number(%) of Subjects with Hematoma/Seroma on Both Sides	Number(%) of Subjects with No Hematoma/Seroma on Either Side
2 (1.7)	14 (11.7)	3 (2.5)	101 (84.2)

Table 13: Comparison of proportions of subjects with haematoma/seroma during both studies

Hematoma/Seroma on FS VH S/D 4 Side	Hematoma/Seroma on Standard of Care Side	Difference in Proportions	95% CI[a]
0.017	0.117	0.100	0.035 to 0.172

[a] 95% confidence interval for difference of paired proportions is based on Newcombe's Method 10.

Safety

A total of 120 subjects received Artiss in the two studies. The mean dose applied was 2.5 mL, with a range of 0.6 to 4.0 mL.

For the pivotal study, adverse events occurring on the face are summarised in Table 9.

For the Phase II study adverse events occurring on the face are summarised in Table 10.

These data suggest that use of Artiss does not result in any noticeable increase in the incidence of adverse events. No new safety issues were raised by the submitted studies.

Risk management plan

The Risk Management Plan submitted with the application was found to be acceptable by the TGA's Office of Product Review.

Risk-benefit analysis

Delegate considerations

Balance of benefits and risks

The two studies demonstrate that use of Artiss results in a decreased volume of postoperative drainage, presumably reflecting a greater extent of adherence of the skin flap. In the draft PI submitted with the application the sponsor has included the following sentence:

The drainage amount observed may preclude the need for drain placement.

This claim is not supported by the submitted data, as the trials included bilateral drain placement and use of Artiss without drain placement has not been tested. Drainage from the Artiss treated side was up to 39 mL in the first 24 hours in the pivotal study and up to 50 mL in the first 24 hours in the Phase II study. These are both above the 30 mL/24 hours level at which the sponsor claims surgical drains can be removed. The reduced volumes may enable earlier removal of drains but this endpoint was not studied in the submitted trials.

As indicated above the combined analysis of the two studies indicates that use of Artiss is associated with a decreased proportion of patients who experience haematoma or seroma. In addition, the pivotal study indicated that patients expressed a preference for the side of the face treated with Artiss. As facelift surgery is a cosmetic procedure, this patient assessment of outcomes is important.

There were no safety concerns arising from the addition of Artiss to standard surgical treatment. The Delegate therefore considered that the benefits of Artiss outweigh its risks in the new indication and proposed to approve the application.

Indication

Based on the submitted studies the sponsor has proposed a broad indication:

To adhere skin flaps and grafts during facial plastic and reconstructive surgery.

As the evidence is limited to use in facial rhytidectomy, the Delegate proposed to restrict the indication to the following, which is the same as that approved in the USA:

To adhere tissue flaps during facial rhytidectomy surgery (facelift).

The Delegate proposed to approve the application with the amended indication outlined above.

Response from Sponsor

The sponsor accepted the Delegate's recommendation to revise the wording of the indication as follows (changes are in bold font):

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

Artiss is indicated to adhere ***tissue flaps during facial rhytidectomy surgery (facelift)****.*

The sponsor also accepted all of the Delegate's recommendations to revise the Product Information (PI) and Consumer Medicine Information (CMI) documents.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy and safety

The ACPM agreed with the Delegate that efficacy has been demonstrated.

Indication

The ACPM considered this product to have a positive benefit risk profile for the indication of:

To adhere tissue flaps during facial rhytidectomy surgery (face-lift).

The ACPM also made a number of recommendations regarding the PI and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

The ACPM advised that the implementation by the sponsor of the recommendations to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for ARTISS would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Artiss for the additional indication of:

To adhere tissue flaps during facial rhytidectomy surgery (face-lift).

Among specific conditions of registration, was the implementation of the Risk Management Plan version, dated February 2011 (Australian version 001) together with any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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