

Summary Basis for Regulatory Action

Date	August 8, 2011
From	Mitchell Frost, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA Supplement#	STN 125266/194
Applicant	Baxter Healthcare Corporation
Date of Submission	October 29, 2010
PDUFA Goal Date	August 29, 2011
Proprietary Name / Established (USAN) names	ARTISS/Fibrin Sealant (Human)
Proposed Indication(s)	To adhere tissue flaps during facial rhytidectomy surgery (face-lift).
Recommended Action:	Approval *ARTISS has already been approved to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and pediatric populations since 2008
Signatory Authorities Action:	<p>Approval</p> <p>Basil Golding _____ <i>Offices Signatory Authority:</i></p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p> <p>John Eltermann _____ <i>Offices Signatory Authority:</i></p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p>

Reviewer Names
Clinical Review: Mitchell Frost
Statistical Review: Boris Zaslavsky
CMC Review: Laura Wood
Epidemiology: Not applicable

Pharmacology/ Toxicology Review: La’Nissa Brown-Baker
Biomonitoring Review: Lillian Ortega
Facilities review: Not applicable
Advisory Committee Transcript: Not applicable
Labeling (Advertising and Promotion): Loan Nguyen
Regulatory Project Manager: Jie He

1. Introduction

This submission is a Biologics License Prior Approval Supplement (PAS) from Baxter Healthcare Corporation (Baxter) to the Biologics License Application (BLA) for Fibrin Sealant (Human) (ARTISS; STN 125266). ARTISS is available in frozen and lyophilized formulations, and has been licensed since 2008 in the United States for topical administration to promote adherence of autologous skin grafts to surgically prepared wound beds, resulting from burns, in adult and pediatric populations greater than or equal to one year of age. ARTISS is nearly identical to Baxter’s licensed fibrin sealant (TISSEEL; STN 103980), the difference being a reduced concentration of thrombin in ARTISS (4 IU/mL) vs. TISSEEL (500 IU/mL).

Baxter has conducted two clinical trials under IND -(b)(4)- in order to expand the current indication to include a new indication: to promote adherence of tissue flaps during facial rhytidectomy surgery.

The recommended dosage of ARTISS and route of administration for the new indication is the same as the current label which states that “the required dose of ARTISS depends on the size of the surface to be covered”. The approximate surface area covered by ARTISS is 100 cm²/2 mL.

2. Background

Fibrin sealants mimic the final stage of the blood coagulation cascade via the combination of concentrated solutions of thrombin and fibrinogen. The concentration of thrombin directly influences coagulation properties. ARTISS, made from pooled human plasma, has a reduced concentration of thrombin in comparison to other fibrin sealants that are indicated as an adjunct to hemostasis. ARTISS is not indicated as an adjunct to hemostasis. Due to the low thrombin concentration, polymerization of ARTISS takes approximately 60 seconds, allowing for time to further manipulate the tissues prior to their adherence and fixation.

Facelift surgery, or rhytidectomy, involves creating tissue flaps via the “lifting-off” of multiple tissue layers (i.e., skin, subcutaneous and muscular layers) from their underlying attachments, over various extents of the face, jaw line and neck. This manipulation of the tissues creates a potential space between the overlying tissue flaps and its underlying attachments, allowing blood (hematoma) and/or fluid (seroma) to collect postoperatively, which may lead to complications and result in a poor cosmetic outcome. The rationale for

the use of ARTISS during rhytidectomy is to adhere the tissue back to its underlying connections; thereby, theoretically eliminating or reducing the potential space that has been created.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

ARTISS was developed in parallel to TISSEEL Fibrin Sealant, which was approved by FDA on 7 February 2000 (STN 103980). Except for the difference in final thrombin concentration (4 IU/mL vs. 500 IU/mL), the manufacturing process -----(b)(4)-----
-----.

The product contains:

Sealer Protein Solution

- Total protein: 96 – 125 mg/mL
- Fibrinogen: 67 – 106 mg/mL
- Fibrinolysis Inhibitor (Aprotinin [Synthetic]): 2250 – 3750 KIU/mL

Thrombin Solution

- Thrombin (Human): 2.5 – 6.5 units/mL
- Calcium Chloride: 36 – 44 µmol/mL

The sealer protein (containing fibrinogen) is manufactured from Source Plasma (Human) that has been tested for the presence of a number of infectious agents. The product is purified by a -----(b)(4)----- . It undergoes solvent detergent treatment and vapor heat treatment to inactivate viruses.

The thrombin component is also manufactured from Source Plasma (Human). It is --- (b)(4) --- purified by -----(b)(4)----, activation of prothrombin, and -----(b)(4)-----
----- steps; it undergoes both solvent detergent treatment and vapor heat treatment for viral inactivation.

The synthetic aprotinin is produced by -----(b)(4)-----.

The calcium chloride solution is manufactured by -----(b)(4)-----.

ARTISS is presented either as a kit containing the two lyophilized biological components with their respective diluents (aprotinin solution for the Sealer Protein and calcium chloride solution for Thrombin), or as two components frozen in pre-filled syringes (Sealer Protein Solution and Thrombin Solution). Both the freeze-dried and frozen forms are supplied as 2 mL, 4 mL or 10 mL (total volume) pack sizes. Excipients in the Sealer Protein Solution include human albumin, tri-sodium citrate, histidine, niacinamide, polysorbate 80 and water for injection. The Thrombin Solution also contains human albumin, sodium chloride and water for injection.

Results of stability support a 24 month shelf life for the kit when stored at controlled temperatures from 2°C to 25°C. The reconstitution studies for the kit components show that the Sealer Protein and the Thrombin are stable for 4 hours after reconstitution when stored at room temperature (2°C to 25°C). Results for the frozen components also support a shelf life of 24 months when stored at ≤ -20°C. After thawing, the components remain stable for 14 days at room temperature (15 to 25°C). If the product is removed from the original pouch or warmed to 33-37°C it must be used within 12 hours.

b) CBER Lot Release

As the concentration of the thrombin component is lower in ARTISS than in TISSEEL, CBER considered to place ARTISS on lot release and to test for thrombin potency. It has been noted with other thrombin products that lower concentration doses are sometimes less stable than those with higher concentrations.

Prior to the initial approval of ARTISS in 2008, conformance lot testing had been performed at CBER for thrombin potency in five lots of ARTISS (3 kits and 2 frozen). Potencies were within the required ranges.

The CMC reviewer (Laura Wood) finds that since no changes have been made in the manufacture or testing of the product from the initial approval, and has no objections to approval of the product.

c) Facilities review/inspection

All production sites and major equipment remain the same as at the time of the initial ARTISS approval and -----(b)(4)-----
-----.

----- (b)(4) -----

-----:

- -----
----- (b)(4) -----
- -----
----- (b)(4) -----
-----.
- -----
----- (b)(4) -----.
- -----
----- (b)(4) -----
-----.

approximately 60 seconds. Additional polymerization continues for ----(b)(4)---- after application.

Spray application of ARTISS over the wound bed provides full surface adherence of skin flaps and grafts. Full surface adherence minimizes areas of dead space between the wound bed and applied tissues. Elimination of dead space prevents shear irritation upon movement as well as reduction of the void space under the skin that can host fluid build-up.

b) Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin.

Aprotinin (Synthetic), fibrinolysis inhibitor, is a polyvalent protease inhibitor that prevents premature degradation of fibrin. Free Aprotinin and its metabolites have a half-life of 30 to 60 minutes and are eliminated by the kidney. Preclinical studies with different fibrin sealant preparations simulating the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of aprotinin in the product formulation increases resistance of the fibrin sealant clot to degradation in a fibrinolytic environment

b) Pharmacokinetics

Pharmacokinetic studies have not been conducted as ARTISS is applied only topically and systemic exposure or distribution to other organs or tissues is not expected.

6. Clinical/ Statistical

a) Clinical Program

Baxter conducted two clinical trials, Studies 550703 and 550901, to evaluate the use of ARTISS for tissue plane adherence in subjects undergoing rhytidectomy (facelift surgery). Both studies used standard labeled dose of ARTISS and were designed as split face rhytidectomy studies, where one side of the face was treated with ARTISS as an adjunct to the standard of care (i.e., intraoperative placed drainage tube, staples and/or sutures) and the other side received standard of care (SoC) alone. Thereby, each subject participated in both study arms simultaneously, serving as his/her own control. In each study, a predefined randomization scheme determined the side of the face to be operated on first, and the side of the face that ARTISS would be applied. The post-operative follow-up was 14 days in both studies.

Study 550703, was a phase 2, prospective, randomized, controlled, evaluator-blinded, multicenter study to explore endpoints for the pivotal study. A total of 45 subjects between the ages of 43 to 70 years were enrolled. Based on the findings of this exploratory study, the primary endpoint selected for the pivotal trial was total drainage volume collected for each side of the face at 24 hours post-surgery.

Study 550901, was a phase 3, prospective, randomized, controlled, subject-blinded, multicenter study comparing the safety and efficacy of ARTISS versus SoC. The primary efficacy endpoint was the total drainage volume collected for each side of the face at 24 h (\pm 4 h) post-surgery. A total of 75 subjects between the ages of 40 to 71 years were enrolled.

The primary efficacy endpoint was the total drainage volume collected for each side of the face at 24 h (\pm 4 h) post-surgery.

The secondary efficacy endpoints were:

- Occurrence of hematoma and seroma on each side of the face.
- Comparison of edema between the 2 sides of the face.
- Changes in skin sensitivity on each side of the face.
- Subject preference.

The primary safety endpoint was the incidence of AEs related to ARTISS throughout the study period. There were no secondary safety endpoints

The full analysis (FA) set consists of all randomized subjects who underwent facial rhytidectomy, received investigational product (IP), and provided data for the primary efficacy endpoint. The safety analysis set includes all subjects who underwent facial rhytidectomy and received SoC or SoC plus ARTISS.

The calculation of sample size was based upon data collected during the phase 2 study. As per the statistical review by Dr. Boris Zaslavsky, the calculation assumed a 10% decrease in mean drainage between the 2 sides of the face (13.7 mL) and with a 50% increase over the observed standard deviation of the paired differences (standard deviation = 34.5mL), a sample size of 75 would be required to obtain 91% power. The primary efficacy analysis summarized the 24 h total volume of drainage for each side of the face using descriptive statistics. The difference in drainage volume between the two sides of the face was assessed with a 2-sided paired t-test with an alpha level of 5%. The FA set was used.

Secondary efficacy endpoint assessment of hematoma/seroma compared the proportion of subjects with hematoma/seroma on the SoC side of the face but not on the IP side of the face to those with hematoma/seroma on the IP side of the face but not on the SoC side of the face. As per Dr. Zaslavsky, a sample size of 75 would yield 87% power in a McNemar test with assumed total discordant proportion of 0.23, and difference in discordant proportions between the 2 sides of the face of 0.17. A 95% confidence interval (CI) around the difference in the paired proportions was computed based on Newcombe's Method.

The secondary efficacy endpoint assessment of skin sensitivity from baseline (pre-surgery) was computed for each side of the face on each postoperative day. Summary statistics were computed for differences between the 2 sides of the face in changes in skin sensitivity, with 95% CIs.

Subject preferences and outcomes were summarized and presented descriptively. Safety outcomes were tabulated.

BIMO Inspections

-----With Held due to Privacy Act-----
-----:

[With Held due to Privacy Act]

-----With Held due to Privacy Act-----

Populations Enrolled/Analyzed

The FA and safety sets are comprised of all 75 randomized and treated subjects. The per protocol (PP) set consists of the 69 subjects who met all inclusion/exclusion criteria, were randomized and treated according to the protocol, and adhered to study procedures with no major protocol deviations.

Subject Disposition

A total of 79 subjects were enrolled (signed informed consent) and screened for eligibility according to the inclusion/exclusion criteria. Of these, 2 subjects at a total of 2 sites were screening failures. In addition, 2 subjects at a total of 2 sites requested withdrawal from the study prior to randomization. Therefore, 75 of the 79 enrolled subjects were randomized. All 75 randomized subjects were treated with ARTISS on one side of the face and received SoC on the other, and all 75 completed the study. The number of subjects randomized at each study site ranged from 7 to 12.

There were 6 major protocol deviations reported during the study:

- 1 major deviation – pregnancy test performed > 72 h prior to surgery
- 1 major deviation – sequence of side of the face operated on first (right then left) not the same as the randomization outcome (left then right)
- 4 major deviations – drain not removed within the pre-specified 24 h \pm 4 h window

Efficacy Analyses

Analyses of Primary Endpoint(s)

Comparison of Drainage Volume (mL) at 24 Hours Postoperative / FA (N=75)

Statistic ^a	Standard of Care	ARTISS	Difference	p-value ^a
Mean (SD)	20.0 (11.3)	7.7 (7.4)	12.3 (11.4)	<0.0001
Median	20.0	8.0	11.0	
Min, Max	0.0, 50.0	0.0, 39.0	-17, 40	

Source: Original sBLA, Full Clinical Study Report: 550901, page 88.

^ap-value from two-sided paired t-test with alpha = 5%.

Comparison of Drainage Volume (mL) at 24 Hours Postoperative / PP (N=69)

Statistic ^a	Standard of Care	ARTISS	Difference	p-value ^a
Mean (SD)	20.5 (11.6)	8.0 (7.5)	12.5 (11.8)	<0.0001
Median	20.0	8.0	11.0	
Min, Max	0.0, 50.0	0.0, 39.0	-17, 40	

Source: Original sBLA, Full Clinical Study Report: 550901, page 89.

^ap-value from two-sided paired t-test with alpha = 5%.

The primary endpoint chosen was discussed and agreed upon between FDA and the sponsor during the course of an End-of-Phase 2 meeting. It is an acceptable primary endpoint because: it occurs in most patients who undergo rhytidectomy, with enough variability that lends it to comparison between patients; it is objective and does not rely upon any subjective interpretations of investigators or patients; and it is clinically meaningful in that any therapy that serves to decrease postoperative drainage could potentially decrease the incidence of hematoma/seroma formation, one of the most common postoperative complications following rhytidectomy. These data robustly demonstrate that the use of ARTISS along with SoC is superior to SoC alone.

Analyses of Secondary Endpoints

Number of Subjects with Hematoma/Seroma Anytime During the Study

Analysis Set	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
FA Set (N=75)	2	5	3	65
PP Set (N=69)	2	5	3	59

Source: Original sBLA, Full Clinical Study Report: 550901, page 99.

No subject with hematoma/seroma required reoperation.

Formation of hematoma/seroma, which usually occurs during the first 7 to 10 days postoperatively, is an important metric because, as stated above, it is one of the most common postoperative complications that occur following rhytidectomy and it often leads to an intervention ranging from needle aspiration to operative evacuation. Further, a decrease in postoperative drainage during the first 24 hours, the study's primary endpoint, should lead to decrease in the overall incidence of hematoma/seroma formation. Thereby, capturing hematoma/seroma formation data could provide data that is supportive of the primary endpoint. These data presented here, demonstrate a lower incidence of hematoma/seroma formation among study subjects receiving ARTISS. As the study was not powered to demonstrate this difference statistically, the finding does not support a stand-alone claim but is supportive of the primary endpoint.

Efficacy Conclusion

The clinical trial conducted to support expansion of the current ARTISS indication to include adherence of tissue flaps during facial rhytidectomy surgery met the pre-specified primary endpoint in that the ARTISS treated side of the face was superior to the SoC side of the face by having less drainage at 24 hours post-surgery.

b) Pediatrics

PREA was triggered as a new indication was being sought. Baxter requested a pediatric waiver for all age groups because the procedure (facial rhytidectomy) being studied is only performed in adults as an elective procedure. The pediatric assessment was presented to the Pediatric Review Committee (PeRC) on July 27, 2011. The PeRC agreed with the Division to grant a full waiver because "studies would be impossible or highly impractical since the disease/condition does not exist in the pediatric population".

7. Safety

The safety database consists of all subjects from both studies who underwent facial rhytidectomy and received SoC or SoC plus ARTISS (N=120). Overall the two study populations are similar, as were the two trials; therefore, it was appropriate to pool the safety data for analyses.

Product exposure:

Duration of product exposure was typical of what would be expected for the use in the target population. Follow-up of 14 days following surgery was reasonable given the product's degradation time *in vivo* of 10 – 15 days and that most of the infectious complications would be expected to be seen within this timeframe. Therefore, all tests reasonably applicable were conducted to assess the safety of the product.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Parameter	Pooled Safety Analysis Set (N=120)
Mean Age (SD)	54.7 (7.2) years

Age Range	40 – 71 years
Mean Weight (SD)	66.5 (11.9) kg
Number Female, Male Subjects	113, 7
Race: Number White, Black, Other Subjects	116, 2, 2
Ethnicity: Number Non Hispanic or Latino, Hispanic or Latino	115, 5

Source: Adapted from Original sBLA, Clinical Summary, pages 20-22

There were no deaths reported in either study. There were no dropouts or discontinuations of subjects once exposed to the product.

Nonfatal Serious Adverse Events

Three subjects experienced serious adverse events. Two were local: wound abscess on the ARTISS treated side of the face that was recognized on postoperative day 14 and was treated by operative incision and drainage; and an incidence of basal cell carcinoma on the SoC treated side of the face. A third subject experienced dehydration on the second postoperative day.

Nonfatal serious adverse events that occurred on the face are presented in tabular format.

System Organ Class	Preferred Term	ARTISS Side of Face Number of Subjects	SoC Side of Face Number of Subjects	Both Sides of Face Number of Subjects
Infections and infestations	Wound abscess	1	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Basal cell carcinoma	0	1	0

Source: Original sBLA, Clinical Summary, page 44.

Common Adverse Events

Summary of Subjects with the Non-Serious Adverse Events Occurring on the Face According to MedDRA Terms by Treated Side of Face

System Organ Class	Preferred Term	ARTISS Side of Face Number of Subjects	SoC Side of Face Number of Subjects	Both Sides of Face Number of Subjects
Congenital, familial and genetic disorders	Epidermolysis	0	1	0
General disorders and administration site conditions	Facial pain	0	0	1
	Edema	0	1	3
	Pain	1	0	0
Infections and infestations	Swelling	1	0	0
	Cellulitis	1	0	0
	Oral herpes	0	1	0
	Tongue abscess	0	0	1
Injury, poisoning and procedural complications	Contusion	0	1	0

	Corneal abrasion	0	1	0
	Post procedural hematoma	1	11	NA
	Procedural pain	0	0	1
	Seroma	4	6	NA
	Thermal burn	0	0	1
	Wound dehiscence	1	1	0
Nervous system disorders	Paresthesia	0	0	1
Skin and subcutaneous tissue disorders	Rash	0	0	1

Source: Original sBLA, Clinical Summary, page 48 and 49

NA = Not applicable; Hematoma/seromas occurring simultaneously on both sides of face were reported as two separate AEs.

Local adverse events that were limited to one side of the face and occurred at a frequency $\geq 1\%$ were hematoma and seroma. The ARTISS treated side of the face had 1 subject with hematoma and 4 with seroma. The SoC treated side of the face had 11 subjects with hematoma and 6 with seroma.

Safety Conclusion

The overall safety profile of ARTISS is acceptable.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this Prior Approval Supplement.

10. Labeling

The sponsor's proprietary name, ARTISS, was reviewed at the time of initial approval by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and was found to be acceptable on January 18, 2008. OBRR concurred.

Full Prescribing Information (FPI): APLB reviewed the original FPI submitted by the sponsor. Comments from a promotional and comprehension perspective were provided to OBRR on June 6, 2008. OBRR and APLB comments regarding the FPI were sent to the sponsor on July 19, 2011. A teleconference was held with the sponsor on July 20, 2011. The sponsor subsequently submitted a revised FPI following the teleconference. A second teleconference was held with the sponsor on August 1, 2011 and the sponsor again submitted a revised FPI on August 4, 2011. In a subsequent teleconference the sponsor accepted all of FDA's remaining comments and recommendations.

Carton and immediate container labels were reviewed from a promotional and comprehension perspective with the original application and approved.

Patient labeling/Medication guide: ARTISS will be administered in a surgical setting only. Patient Information is appropriately provided in the Section 17 of the FPI.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of this supplement.

b) Risk/ Benefit Assessment

Efficacy and safety data were found adequate to make a favorable decision concerning potential risk/benefit balance.

c) Recommendation for Post-Marketing Activities

There are no new plans for pharmacovigilance with this efficacy supplement. Pharmacovigilance will continue through passive reporting that has been ongoing since the approval of the original BLA.

d) Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments.