



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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SUBJECT: STN 125266 Baxter Healthcare Fibrin Sealant 4 IU VH S/D Final Review Memo

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I. Summary

Fibrin Sealant with 4IU/ml human thrombin, vapor heated, solvent/detergent treated (i.e. FS 4IU VH S/D) is a double virally inactivated frozen (-20°C) or lyophilized (depending on the presentation), plasma-derived biologic developed by Baxter to adhere autologous skin grafts to surgically prepared wound beds resulting from burns. The two main ingredients are Sealer Protein Solution (human fibrinogen) and Thrombin solution (human thrombin), which are supplied as frozen or lyophilized components that are mixed in equal proportions to produced a viscous fibrin sealant that sets into a white clot. Degradation of the fibrin sealant occurs in vivo by proteolysis and phagocytosis of the course of 10 -15 days.

FS 4IU VH/SD is similar to the currently licensed fibrin sealant, TISSEEL VH S/D except that it has a final thrombin concentration of approximately 4IU rather than 500 IU.

This BLA contains a clinical summary with integrated analyses of efficacy and safety data for study 520001 and study 550201 for the use of FS 4IU VH S/D in burn grafting. The first study, 52001 is a phase 1 / 2 multi-center, prospective, randomized, comparative, feasibility study to assess the safety and efficacy of FS 4IU versus staples for wound healing through the facilitation of surgical closure. Study 550201 is a phase 3 multi-centered, prospective, evaluator blinded, randomized study comparing FS 4 IU VH S/D to staples for use in skin graft adherence and wound healing in subjects with burn wounds.

FS 4 IU and FS 4 IU VH S/D are similar products that differ with respect to the additional solvent/ detergent viral inactivation step used during the manufacture of FS 4 IU VH S/D. Furthermore, FS 4IU VH S/D used in clinical study 550201 (pivotal study) was provided in a frozen formulation , whereas the FS 4 IU used in the phase 1 /2 study was presented in a lyophilized form that required reconstitution prior to use. The sponsor plans to provide FS 4 IU VH S/D in both the frozen and lyophilized forms upon approval of the BLA.

The overall design for both studies was similar involving a comparison of the study product (FS 4IU VH S/D or FS 4IU) to the standard of care (staples). Each subject served as his/her own control and received treatment with both study product and staples at separate test sites. The following were eligibility requirements:

- Deep partial thickness or full thickness burn wounds measuring $\leq 40\%$ total body surface area (TBSA),
- Ages ≥ 6 and ≤ 65 years old (clinical study 520001, subjects in Baxter clinical study 550201 were to be ≤ 65 years old including pediatric subjects of all ages.
- Test sites grafted with autologous sheet skin grafts.
- Test sites had to be either a single wound measuring between 2% and 8% TBSA that could be split into 2 halves or 2 comparable wounds each measuring between 1% and 4% TBSA.

Wound beds of both test sites were prepared prior to treatment assignment. In accordance with the predetermined randomization scheme, study product was to be used to affix skin grafts at one test site (treatment), and staples to affix skin grafts at the other test site (control). Each subject was to serve as his/her own control.

The postoperative follow-up was planned for 1 year in both studies: Baxter clinical study 520001 comprised an initial 3-month follow-up (Day 0 [grafting], Day 1, Day 5, Day 14, Day 21, Day 28, Day 35, Day 49, Day 64, and Day 91 assessments), followed by a long-term cosmetic evaluation through to the Month 12 end-of-study visit (Month 6, Month 9, and Month 12 assessments). Baxter clinical study 550201 comprised an initial assessment of the primary efficacy endpoint and the secondary efficacy endpoints measured up to Day 28 (Part A), followed by the long-term cosmetic follow-up that is still ongoing (Part B). The assessments for Baxter clinical study 550201 were scheduled for Day 0 [grafting], Day 1, Day 5, Day 14, Day 28, Month 3, Month 6, Month 9, and Month 12.

The main difference between the 2 studies was the use of a blinded review panel to assess the primary efficacy of endpoint of complete wound closure by Day 28 in Baxter clinical study 550201. A panel of 3 independent experts, blinded with respect to treatment assignment, reviewed photographs of the test sites in a random order and assessed whether complete wound closure had occurred (success) or not (treatment failure). In contrast, all efficacy endpoints in Baxter clinical study 520001 were assessed by the investigator at the time of examination.

The study met its primary endpoint of non-inferiority of FS 4 IU VH S/D to staples for wound closure by day 28. The study results did not suggest a safety concern for use of FS 4IU VH S/D in the burn graft clinical setting.

II. Phase 2 Study (520001)

An exploratory study that involved 40 treated subjects who were analyzed as a single intent-to-treat population (ITT).

Title:

“A Study To Evaluate the Safety and Efficacy of Fibrin Sealant with 4 IU/mL Thrombin, Vapor Heated, Solvent Detergent Treated (FS 4IU VH S/D) to Adhere Tissues and Improve Wound Healing”

Indication Studied:

Tissue adherence and wound healing

Objectives:

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 4 IU to those affixed with staples;
3. To compare surgical closure for grafts affixed with FS 4 IU 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 4 IU 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.

Study Design:

Phase 1/2, multi- center, prospective, randomized, 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 randomization scheme, 1 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.

Baxter clinical study 520001 was composed of 2 study evaluation periods: 1) An initial 3-month follow-up for all subjects; 2) A 9-month extension for all subjects who achieved surgical closure in 1 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 hematoma 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 1 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 1 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. In addition, adverse experiences and concomitant medications were recorded throughout the study. This report provides results of the 3-month follow-up through Day 91, and data for those subjects who enrolled in the 9-month extension.

Study Duration:

First subject enrolled: 7 March 2002

Last subject completed 3 –month follow-up: 30 April 2003

Last subject completed 9-month extension: 20 January 2004

Diagnosis and main inclusion criteria:

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.

Exclusion criteria:

1. Conductive electrical burns and chemical burns
2. Digits, head, genitalia, palms of hands, soles of feet, and face are excluded as test sites
3. Circumferential burns are excluded as a test area
4. 4th or 5th degree burns
5. Test area with infection, as determined clinically by the investigator
6. Venous or arterial vascular disorder directly affecting a designated test area
7. Known immune deficiency disorder, either congenital or acquired,
8. Chronically malnourished, as determined clinically by the investigator prior to surgery (Investigators were responsible for determining if subjects were chronically malnourished during the screening process. Investigators were to take into consideration the following parameters: medical history and physical appearance, the subject's body mass index, and any significant laboratory findings)

9. Severe respiratory problems or concurrent head trauma at hospital Admission
10. Any chronic condition requiring the use of systemic corticosteroids 30 days prior to study entry and anytime during the course of the study
11. Known or newly diagnosed diabetics requiring insulin
12. Any other acute or chronic concurrent medical condition(s) that in the investigator's opinion is (are) a contraindication to skin grafting and study participation
13. Known or suspected hypersensitivity to bovine protein
14. Concurrent participation in another clinical trial in which an investigational agent is used (Subjects must not have been enrolled in another clinical trial within 30 days of enrolling in this trial).

Test Product, dose and mode of administration:

Fibrin sealant with 4 IU / ml Thrombin (FS 4 IU)

Dose: 0.04 to 0.06 ml/cm² (recommended and approximate dose to be applied)

Mode of administration: Spray application via the TISSOMAT and Spray set device

Subjects were treated once intraoperatively at one designated test site. The total period of study participation was 3 months if closure was not achieved in either test site after surgery, or 12 months if surgical closure was achieved in 1 or both test sites.

Control treatment and mode of administration:

Staples

Mode of administration: Mechanical/ point fixation

Treatment Administered

Each subject had either a single contiguous burn wound area measuring between 2% and 8% TBSA that was divided into 2 approximate halves, or 2 bilateral burn wounds (each measuring between 1% and 4% TBSA). Test sites were selected and labeled (Test Site A and Test Site B) before randomization to FS 4IU or staples. Randomization was based on a predetermined randomization scheme for each study site

FS 4IU was administered intraoperatively by spray application using the TISSOMAT and Spray set. Only the DUPLOJECT system and Spray Set (connection tube with sterile filter and spray head) device was used for simultaneous spray application of the 2 solutions of the study product. A thin layer of FS 4IU was applied to the wound bed using a painting motion from side to side to achieve coverage. The recommended volume per application was approximately 0.04 to 0.06 mL/cm².

Concomitant Medications

Concomitant medications were documented in the subject's clinic/hospital and study records using the guidelines set forth by the Sponsor and on the appropriate CRFs. During the grafting surgery, the use of topical thrombin spray or another fibrin sealant to achieve hemostasis was prohibited. In addition, any method of fixation (e.g., pressure, steri-strips, or staples) as part of the surgical technique to

help anchor skin grafts were removed prior to dressing the test area.

Schedule of Events:

Table 9.5-2			
Schedule of Safety Observations and Clinical Assessments for the 9-Month Extension			
Study Procedures	Postoperative		
Safety Observations	Month 6	Month 9	Month 12
Concomitant Medications	X	X	X
Adverse Experiences	X	X	X
Clinical Assessments			
Photography	X	X	X
Vancouver Scar Scale	X	X	X
Incidence of Keloid Formation and Hypertrophic Scarring	X	X	X

Criteria for Evaluation:

Efficacy:

Efficacy was evaluated by the following:

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

- surgery
- Incidence of keloid formation and hypertrophic scarring

Safety:

The overall safety of FS 4IU was assessed by the incidence and severity of adverse experiences and changes in vital signs, clinical, and laboratory parameters.

Statistical Methods

The comparison of paired quantitative efficacy results (within subject) was made using the Wilcoxon signed rank test. The frequency of surgical closure and other categorical outcomes were evaluated using McNemar’s test. Safety outcomes were tabulated.

Study Results:

Subject Disposition

A total of 40 subjects were enrolled at 9 of the 12 participating study sites. The number of subjects enrolled at each study site ranged from 2 to 8.

Table 14.1- 2 Subject Disposition

Population	N (%)
Total Randomized	40/40 (100.0%)
Completed through Day 21 ^a	38/40 (95.0%)
Completed 3 Month Follow- up	31/40 (77.5%)
Entered 9 Month Extension ^b	30/31 (96.8%)
Completed 9 Month Extension	20/30 (66.7%)
Discontinuation Reason	
Lost to Follow- up ^c	17/40 (42.5%)
Other ^d	2/40 (5.0%)
Total^e	19/40 (47.5%)

The following table is a summary of the demographic characteristics of the subjects:

Table 14.2- 3 Summary of Demographic Characteristics and TBSA of Burn Wound

Characteristic	Value
Gender [N (%)]	
Male	29 (72.5%)
Female	11 (27.5%)
Age (years)	
Mean (StD)	30.5 (14.19)
Median	32.7
Range	6.2 - 54.6
6 thru 18 years [N(%)]	8 (20.0%)
Over 18 years [N(%)]	32 (80.0%)
Race [N (%)]	
Caucasian	36 (90.0%)
Black	4 (10.0%)
Hispanic/Latino origin[N (%)]	9 (22.5%)
Wt (kg)	
Mean (StD)	68.1 (23.68)
Median	69.8
Range	21.0 - 136.2
Height (cm)	
Mean (StD)	165.1 (20.94)
Median	172.7
Range	110.0 - 185.4
Estimated TBSA for all burns (%)	

The estimated mean \pm SD Total Body Surface Area (TBSA) for each subject's entire test area was 15.6% \pm 9.62% (range: 3 to 40%). The estimated mean \pm SD TBSA for each subject's entire test area was 3.2 \pm 1.26% (range 2 to 8%). Twenty-six (65%) of the burn wounds were full thickness and 14 (35%) were partial thickness.

Table 14.2-9 Summary of Efficacy Endpoints:

Endpoint	N	FS 4IU	Staples	P- Value
		Median (Min- Max)	Median (Min- Max)	
% Area of overall graft survival on Day 14	36	100.0 (65.7 - 100.0)	100.0 (83.2 - 100.0)	0.3525
% Area of Questionable Viability on Day 5	38	0.0 (0.0 - 12.7)	0.5 (0.0 - 100.0)	0.0182
% Area of H/S on Day 1	39	0.0 (0.0 - 17.0)	2.1 (0.0 - 46.4)	0.0138
Number of H/S objects on Day 1	39	0.0 (0.0 - 22.0)	2.0 (0.0 - 18.0)	0.1683
Degree of Contracture on Day 5 (%)	38	6.9 (- 23.5 - 24.7)	- 0.5 (- 43.1 - 31.4)	0.0094
Degree of Contracture on Day 14 (%)	37	18.3 (- 13.0 - 37.0)	14.7 (- 18.6 - 39.5)	0.7731
Degree of Contracture on Day 21 (%)	8	18.2 (0.2 - 34.3)	22.9 (- 7.6 - 43.8)	0.7422
Degree of Contracture on Day 91 (%)	20	24.8 (0.3 - 58.1)	23.7 (- 6.5 - 48.5)	0.7841
Time to surgical closure (days)	32	5.0 (4.0 - 68.0)	5.0 (5.0 - 91.0)	0.2383
Surgical Closure on Day 5 (N (%)) ^a	39	24 (61.5%)	18 (46.2%)	0.0703
Regraft (N (%))	36	2 (5.6%)	4 (11.1%)	0.5000

- 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).
- More FS 4 IU-treated sites (N = 37) closed by Day 91 compared to the corresponding stapled sites (N = 32), and the FS 4 IU-treated sites closed sooner than the stapled sites.
- On Day 5, FS 4 IU-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; 80.0% of subjects with FS 4 IU-treated sites closed, whereas only 59.0% of the subjects with stapled sites closed.
- 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. There were no apparent statistically significant differences between FS 4 IU-treated sites and stapled sites were found for any of the Vancouver Scar Scale properties (i.e. pigmentation, vascularity, pliability, and height) evaluated at the 6, 9, or 12 month visits. Similarly, there were no statistically significant differences between FS 4 IU 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.

The sponsor provided a summary of hematoma and seroma formation according to burn wound type (full or partial thickness) as follows:

Table 14.2- 10 Summary of Efficacy Endpoints According to Burn Wound Type

Efficacy Measure	Burn Wound Type = Full Thickness		Burn Wound Type = Partial Thickness	
	FS 4IU N: Median (Min- Max)	Staples N: Median (Min- Max)	FS 4IU N: Median (Min- Max)	Staples N: Median (Min- Max)
% Area of overall graft survival on Day 14	26: 100.0 (65.7 - 100.0)	24: 98.8 (83.2 - 100.0)	13: 100.0 (96.4 - 100.0)	12: 100.0 (96.2 - 100.0)
% Area of Questionable Viability on Day 5	25: 0.0 (0.0 - 2.5)	24: 0.0 (0.0 - 9.4)	14: 0.0 (0.0 - 12.7)	14: 1.4 (0.0 - 100.0)
% Area of H/S on Day 1	25: 0.0 (0.0 - 17.0)	25: 3.4 (0.0 - 46.4)	14: 0.4 (0.0 - 3.3)	14: 1.4 (0.0 - 8.8)
Number of H/S objects on Day 1	25: 0.0 (0.0 - 22.0)	25: 2.0 (0.0 - 8.0)	14: 0.5 (0.0 - 12.0)	14: 2.5 (0.0 - 18.0)
Degree of Contracture on Day 5 (%)	25: 8.0 (- 23.5 - 24.4)	24: 3.2 (- 43.1 - 31.4)	14: 5.9 (- 2.7 - 24.7)	14: - 1.8 (- 15.2 - 16.2)
Degree of Contracture on Day 14 (%)	26: 19.1 (- 13.0 - 37.0)	25: 17.3 (- 18.6 - 39.5)	13: 10.5 (- 8.7 - 32.8)	12: 10.4 (- 8.8 - 19.9)
Degree of Contracture on Day 21 (%)	6: 24.1 (12.0 - 34.3)	7: 23.0 (- 7.6 - 43.8)	3: 2.3 (0.2 - 18.2)	3: 5.3 (- 0.4 - 24.3)
Degree of Contracture on Day 91 (%)	15: 24.8 (0.3 - 58.1)	14: 13.8 (- 6.5 - 48.5)	6: 25.3 (5.8 - 37.8)	6: 31.7 (5.4 - 36.8)
Time to surgical closure (days)	24: 5.0 (4.0 - 68.0)	21: 5.0 (5.0 - 91.0)	13: 5.0 (5.0 - 32.0)	11: 5.0 (5.0 - 68.0)
Surgical Closure on Day 5 (N (%)) ^a	14/26 (53.8%)	11/26 (42.3%)	9/13 (69.2%)	7/13 (53.8%)

- The median percent area of hematoma and seroma formation on Day 1 for full thickness burn wounds was 0% (range 0-17%) for FS 4IU treated sites and 3.4% (range 0-46.4%) for staples sites. The median percent area of hematoma and seroma formation on day 1 for partial thickness burns was 0.4% (range: 0 to 3.3%) for FS 4 IU treated sites and 1.4% (range: 0-8.8%) for staples sites.

Exploratory analyses compared surgical closure on Day 5 for FS 4IU-treated and stapled sites using alternate definitions of surgical closure. When surgical closure was defined in an alternative manner (> 95% graft survival on Day 14 and 0% area of questionable viability on Day 5), surgical closure was achieved in 24/38 (63.2%) FS 4IU-treated sites compared with 17/38 (44.7%) stapled sites (p = 0.0654). Paired analysis of wound closure by Day 28 was also performed. Wound closure by Day 28 was achieved in 31/39 (79.5%) of FS 4 IU-treated sites compared with 23/39 (59.0%) stapled sites, which is a statistically significant difference (p = 0.0215).

Table 14.2- 14 Analysis of Surgical Closure Definitions

Surgical Closure Definition	FS 4IU n/N (%)	Staples n/N (%)	P- Value
100% Graft Take on Day 14 ^a	24/39 (61.5%)	18/39 (46.2%)	0.0703
100% Graft Take on Day 14 and 0% Area of Questionable Viability on Day 5	19/38 (50.0%)	14/38 (36.8%)	0.1797
>=95% Graft Take on Day 14	34/36 (94.4%)	30/36 (83.3%)	0.1250
>=95% Graft Take on Day 14 and 0% Area of Questionable Viability on Day 5	24/38 (63.2%)	17/38 (44.7%)	0.0654
Wound Closure by Day 28	31/39 (79.5%)	23/39 (59.0%)	0.0215

Overall percent graft survival on Day 14 and time to surgical closure were similar for the 2 treatments, demonstrating that FS 4IU is comparable and equivalent to the staples. FS 4 IU treated sites had significantly fewer areas of hematoma and seroma and questionable viability on Day 5, indicating fewer complications and early vascularization of the skin graft. The proportion of sites deemed surgically closed on Day 5 was higher in FS 4IU-treated sites than stapled sites, indicating that FS 4IU could shorten the time required for closure. Additionally, a higher percentage of FS 4IU-treated sites were surgically closed at each study visit after Day 14. Paired analysis of wound closure at

Day 28 demonstrated that complete closure was achieved in significantly more FS 4 IU-treated sites than stapled sites.

Safety

A total of 423 adverse experiences were reported in 40 subjects. 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 the serious adverse experiences were considered by the Investigators or the sponsor to be related to the use of FS 4 IU.

Of the reported adverse experiences, the serious ones, N= 6 (1.4%) were judged by the investigators to be possibly related to the use of FS 4 IU. These events include intestinal perforation (N= 1), post operative infection (N=4), delirium tremens (N=1). The post operative donor site infections required hospitalization in 4 patients.

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.

There were 417 non serious adverse events 296 (70%) reported in 37 subjects were rated mild, 116 (27.4%) reported in 26 subjects were rated moderate, and 5 (1.2%) reported in 5 subjects were rated severe. The 5 severe non serious adverse events included 4 incidences of pain at the graft site and 1 incidence of graft loss.

Site 11 (Kevin Foster, Maricopa Medical Center, enrolled 3 subjects) reported 5 cases of hematoma and seroma that were regarded as related to study product due to the temporal relationship of the seroma/hematoma to study product administration.

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 1 or both test sites. Among these event types, there was no apparent difference in the frequency of occurrence at FS 4 IU-treated or stapled sites. A total of 75 events were localized to FS 4 IU-treated sites and 92 were localized to stapled sites.

Table 14.3- 7 Adverse Experiences Occurring at One or Both Test Sites

Preferred Term	FS 4IU n/N (%)	Staples n/N (%)	Neither ^a n/N (%)	Total n/N ^b (%)
Abscess	0/ 1 (0.0 %)	1/ 1 (100.0 %)	0/ 1 (0.0 %)	1/ 1 (100.0 %)
Blister	2/ 7 (28.6 %)	2/ 7 (28.6 %)	3/ 7 (42.9 %)	7/ 7 (100.0 %)
Cellulitis	1/ 4 (25.0 %)	0/ 4 (0.0 %)	3/ 4 (75.0 %)	4/ 4 (100.0 %)
Excoriation	3/ 7 (42.9 %)	2/ 7 (28.6 %)	2/ 7 (28.6 %)	7/ 7 (100.0 %)
Folliculitis	1/ 1 (100.0 %)	0/ 1 (0.0 %)	0/ 1 (0.0 %)	1/ 1 (100.0 %)
Graft complication	1/ 2 (50.0 %)	1/ 2 (50.0 %)	0/ 2 (0.0 %)	2/ 2 (100.0 %)
Graft loss	19/ 49 (38.8 %)	22/ 49 (44.9 %)	8/ 49 (16.3 %)	49/ 49 (100.0 %)
Haematoma	20/ 48 (41.7 %)	28/ 48 (58.3 %)	0/ 48 (0.0 %)	48/ 48 (100.0 %)
Hypertrophic scar	1/ 2 (50.0 %)	1/ 2 (50.0 %)	0/ 2 (0.0 %)	2/ 2 (100.0 %)
Limb injury	1/ 1 (100.0 %)	0/ 1 (0.0 %)	0/ 1 (0.0 %)	1/ 1 (100.0 %)
Muscle cramp	1/ 3 (33.3 %)	1/ 3 (33.3 %)	1/ 3 (33.3 %)	3/ 3 (100.0 %)
Pain	2/ 19 (10.5 %)	2/ 19 (10.5 %)	15/ 19 (78.9 %)	19/ 19 (100.0 %)
Pain in extremity	1/ 5 (20.0 %)	1/ 5 (20.0 %)	3/ 5 (60.0 %)	5/ 5 (100.0 %)
Pruritus	8/ 36 (22.2 %)	8/ 36 (22.2 %)	20/ 36 (55.6 %)	36/ 36 (100.0 %)
Seroma	13/ 34 (38.2 %)	21/ 34 (61.8 %)	0/ 34 (0.0 %)	34/ 34 (100.0 %)
Staphylococcal infection	1/ 2 (50.0 %)	1/ 2 (50.0 %)	0/ 2 (0.0 %)	2/ 2 (100.0 %)
Stitch abscess	0/ 1 (0.0 %)	1/ 1 (100.0 %)	0/ 1 (0.0 %)	1/ 1 (100.0 %)
Total	75/222 (33.8 %)	92/222 (41.4 %)	55/222 (24.8 %)	222/222 (100.0 %)

Examination of vital signs, hematology, and clinical chemistry parameters did not reveal safety concerns for FS 4 IU. Adverse experiences reported for FS 4IU-treated sites were typical for the type of injury sustained by subjects with burn wounds requiring skin grafting procedures. Changes in vital signs, hematology and clinical chemistry parameters showed no evidence of toxicity.

Regrafting

Of the 36 test sites 2, (5.6%) FS 4 IU treated sites and 4 (11.1%) stapled sites were regrafted. Regrafting included full or partial regrafting and patch grafting.

III. Phase 3 Study (550201)

127 ITT subjects. The ITT population of Baxter clinical study 550201 included 127 of the 138 treated subjects. The 11 treated subjects not included in the ITT population were excluded for one of the following reasons: no primary endpoint assessment at both test sites; lost to follow-up prior to Day 28; or photographs not taken at both test sites on Day 28. The per protocol (PP) population consisted of the 106 subjects who met the criteria defined for the PP population in the *a priori* statistical analysis plan.

Title: A Study To Evaluate the Safety and Efficacy of Fibrin Sealant with 4IU/mL Thrombin, Vapor Heated, Solvent Detergent Treated (FS 4 IU VH S/D) to Adhere Tissues and Improve Wound Healing

Objectives:

The overall objective of this Phase 3 study was 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 4 IU 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 4 IU VH S/D in grafting procedures results in non-inferior graft adherence and wound healing when compared to the use of staples.

Study Design:

A Phase 3, multi-centered, prospective, evaluator blinded, randomized study comparing FS 4 IU VH S/D to staples. 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 be split into 2 comparable test sites. After test site selection, FS 4 IU 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) in accordance with the predetermined randomization scheme. The postoperative follow-up was planned for 1 year. The day of the skin grafting procedure, when FS 4 IU VH S/D and staples were used, was designated as Day 0. Subjects were required to undergo evaluations and study procedures at Screening and on Day 0, 5, 14, and 28 and Month 3, 6, 9, and 12 visits.

The study was divided into 2 reporting parts: Part A, which includes the primary endpoint analysis, and Part B, a follow-up of cosmetic outcomes through Month 12. This clinical study report serves to report the data collected in Parts A and B.

Inclusion Criteria

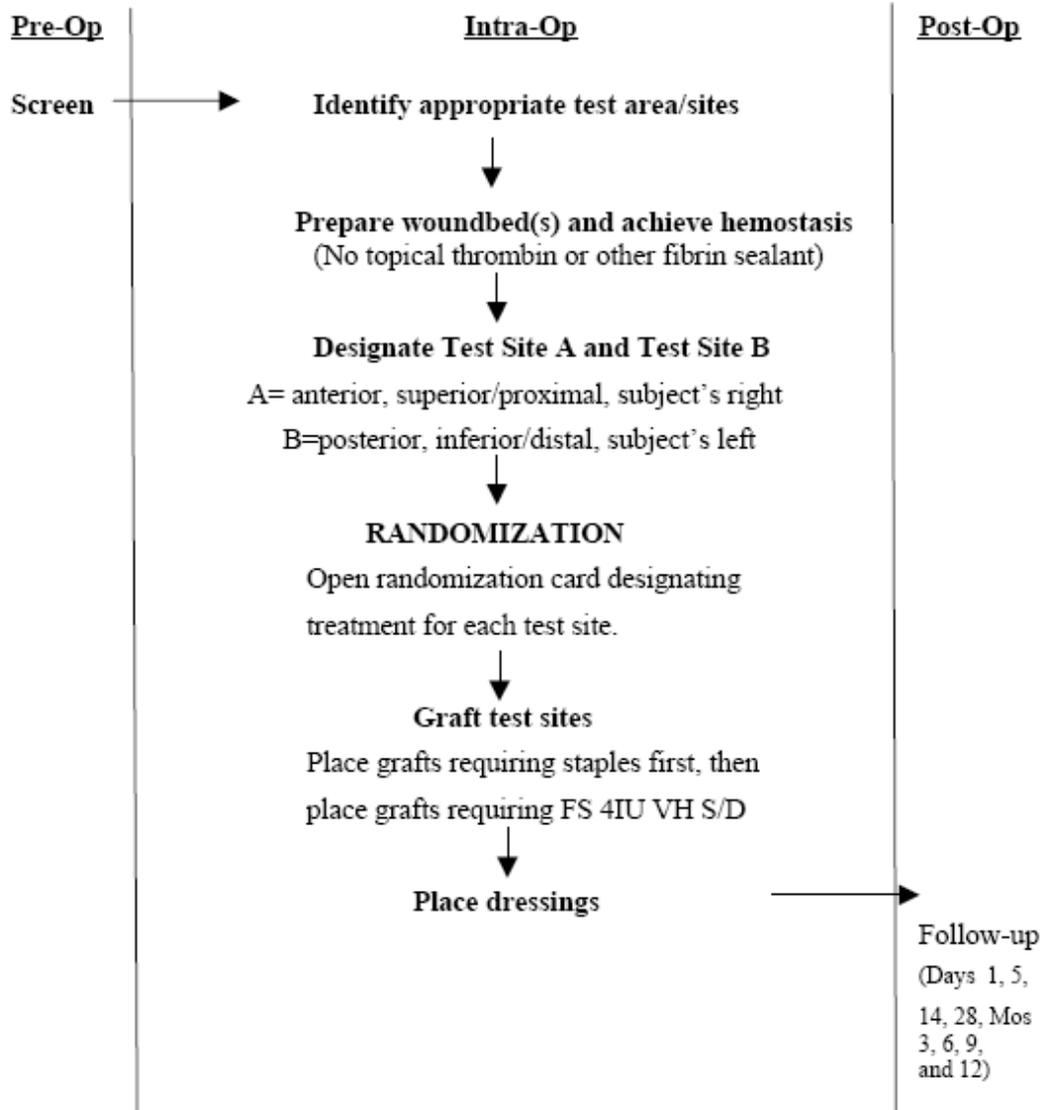
- Subjects or their legal representatives, who have read, understood and signed a written informed consent.
- Subjects of either sex.
- Female subjects of childbearing potential with a negative urine or serum pregnancy test within 24 hours prior to surgery.
- Subjects who are ≤ 65 years of age including pediatric subjects of all ages.
- Subjects with total burn wounds measuring $\leq 40\%$ TBSA.
- Subjects with a contiguous deep partial thickness/full thickness wound, between 2% and 8% TBSA or two comparable, bilateral wounds each measuring between 1% and 4% TBSA.

- Wounds designated as test sites require autologous sheet skin grafts with a thickness of 8/1000 of an inch to 16/1000 of an inch
- Subjects who are able, and willing to comply with the procedures required by the protocol

Exclusion Criteria

- Subjects with electrical burns.
- Subjects with chemical burns
- Digits and genitalia are excluded as test sites.
- Subjects with infection at test area/test sites.
- Subjects with test sites previously randomized and treated in this study.
- Subjects with venous or arterial vascular disorder that directly affects a designated test area/test site.
- Subjects with pre-existing hemolytic anemia
- Subjects with diabetes mellitus.
- Subjects with documented history of pathologically or pharmacologically induced immune deficiency.
- Subjects judged to be chronically malnourished.
- Subjects that are judged to have significant pulmonary compromise.
- Subjects receiving systemic corticosteroids within 30 days prior to skin grafting (not including inhaled steroids).
- Subjects with known or suspected hypersensitivity to bovine proteins.
- Subjects participating in another clinical trial that is evaluating an unapproved drug or device.

Schematic Overview of Procedure Study Design



See Section 13.1 for a complete schedule of study assessments.

Diagnosis and Main Criteria for Inclusion:

Subjects ≤ 65 years of age (including pediatric subjects) with total burn wounds measuring $\leq 40\%$ TBSA were eligible for treatment under this protocol. Subjects with electrical or chemical burns were excluded. Eligible subjects were required to have deep partial thickness or full thickness wounds. The test area could be either a single wound

measuring between 2% and 8% TBSA that could be split into 2 test sites each measuring 1% to 4% TBSA or 2 separate wounds each measuring between 1% and 4% TBSA, and providing comparable test sites. Burn wounds on digits or genitalia were not eligible for designation as a test site. Autologous sheet skin grafts with a thickness of 8/1000 of an inch to 16/1000 of an inch were to be used.

Main Exclusion Criteria

- Subjects with electrical burns.
- Subjects with chemical burns
- Digits and genitalia are excluded as test sites.
- Subjects with infection at test area/test sites.
- Subjects with test sites previously randomized and treated in this study.
- Subjects with venous or arterial vascular disorder that directly affects a designated test area/test site.
- Subjects with pre-existing hemolytic anemia
- Subjects with diabetes mellitus.
- Subjects with documented history of pathologically or pharmacologically induced immune deficiency.
- Subjects judged to be chronically malnourished.
- Subjects that are judged to have significant pulmonary compromise.
- Subjects receiving systemic corticosteroids within 30 days prior to skin grafting (not including inhaled steroids)
- Subjects with known or suspected hypersensitivity to bovine proteins
- Subjects participating in another clinical trial that is evaluating an unapproved drug or device

Treatments:

Test Product: FS 4 IU VH S/D, a two component fibrin sealant with 4 IU/ml human thrombin, vapor heated, solvent detergent treated, provided in a frozen, ready to use formulation.

To maintain some consistency, a maximum of two surgeons per center were allowed to select and graft the test sites; other arrangements required the sponsor's approval. Skin grafting could be performed during the same surgical session as debridement and excision (one stage procedure) or at a later time point (two stage procedure). Skin grafts were to be harvested according to the standard of care for each individual institution. However, all grafts were to be harvested as autologous partial thickness, sheet skin grafts with a thickness of 8/1000 of an inch to 16/1000 of an inch. No full thickness grafts were allowed.

In addition to the test area requirements of being either a single contiguous wound area measuring between 2% and 8% TBSA, or 2 separate/bilateral wounds each measuring between 1% and 4% TBSA, the test sites selected were also to be consistent with the following criteria:

- The 2 test sites, whether one contiguous wound or two separate wounds, were required to be comparable in terms of size, depth of burn, and type of skin surface. Mobile areas were to be compared to mobile areas; non-mobile areas were to be compared to non-mobile areas; arms were to be compared to arms and legs were to be compared to legs. Anatomically, each designated test site was to have the same shear force potential.

- A proportion of a contiguous burn wound larger than the maximum allowable TBSA could be used as a test area/test site(s) as deemed appropriate by the Investigator to reduce the amount of donor skin harvested and to obtain the best result for the subject. Staples or other methods used to affix abutting grafts were to be placed parallel to the test site seams and could not encroach upon the FS 4IU VH S/D test site.
- Circumferential burns could be included as test sites. If the area was to be split into 2 halves, each half should have been split so that each contains a circumferential wound, ensuring that all surfaces were equally represented in both test sites. In addition, an area between 1% and 4% of a circumferential area could be isolated as

The designated area for study was to be tangentially excised, forming a uniform wound bed. Hemostasis was to be achieved within the wound beds prior to grafting of the test area using tourniquets, cautery, or gauze sponges soaked in epinephrine and /or lidocaine.

Topical thrombin was excluded in the wound beds of areas designated as test sites. Fibrin sealants other than the FS 4 IU VH S/D to which a subject was randomized were not permitted to be used.

Hematomas /Seromas

In accordance with the institution's standard of care and at the discretion of the investigator, hematomas/seromas were required to be appropriately expressed at the Day 1 visit after assessments had been made and photographs had been taken. Expression of hematomas/seromas was to be recorded. Once dressings were changed, they were not to be removed until the postoperative Day 5 visit unless deemed medically necessary. However, if medically necessary, an additional dressing change between the first dressing change on Day 1 (± 1) and Day 5 (± 1) was allowed.

Regrafting

For purposes of this study, regrafting (including patch grafting or full/partial regrafting) was considered a treatment failure for the primary endpoint of complete wound closure at Day 28. Subjects with one or both test sites regrafted were to remain in the study for the full one-year follow-up period. If only one test site was regrafted, the regrafted test site was to be considered "not closed" and the non-regrafted test site was required to be evaluated for complete wound closure at Day 28. If one or both test sites were regrafted, the subject was required to have both test sites photographed at Day 28 and have Vancouver Scar Scale evaluations performed, in addition to global photographs at Month 3, 6, 9, and 12 visits. Planimetry assessments were not required for regrafted test sites.

Dose: Actual mean dose calculated for FS 4 IU VH S/D was 1.8 ± 1.1 ml/100 cm². Median calculated dosing volume = 1.5 ml/ 100 cm²; range: 0.2 to 6.0 ml/100 cm². The mean surface area treated \pm SD was 166.4 ± 95.0 cm² (median surface area treated = 142.3 cm²; range: 26.1 to 602.7 cm²). The mean volume \pm SD applied was 2.7 ± 1.9 ml (median volume applied = 2.4 ml; range: 0.2 to 12. 0 ml).

Mode of administration:

Topical spray application using the TISSOMAT device and Spray Set

Duration of treatment:

Subjects were treated with one dose of FS 4IU VH S/D intraoperatively at one test site and with staples at the other test site, according to a prespecified randomization schedule.

Criteria for Evaluation:**Efficacy****Primary Efficacy Endpoint:**

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

Note:

Complete wound closure was defined as total coverage of the wound with a contiguous layer of viable epithelium; areas closing by secondary intention also had to be fully closed. Factors considered during this assessment included color, presence of granulation tissue, and whether or not the entire wound was covered with a contiguous layer of viable epithelium.

Secondary Efficacy Endpoints:

- Presence of hematoma/seroma on Day 1
- Percent area of hematoma/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

Safety**Primary Safety Endpoint:**

- Adverse experiences (AEs) deemed possibly or probably related to treatment with FS 4IU VH S/D

Secondary Safety Endpoints:

- There were no secondary safety endpoints

Statistical Methods:

The primary efficacy endpoint was complete wound closure by Day 28 as determined by the majority opinion of a panel of 3 experts who evaluated photographs of the test sites. Photographs were presented to the panel members in a random, blinded manner, with each of the 3 reviewers attending separate sessions in an attempt to avoid bias.

The primary efficacy analysis was performed on the intent-to-treat population. The intent-to-treat population consisted of all subjects with at least one available primary endpoint assessment. In addition, an efficacy analysis was done on those subjects deemed evaluable per protocol (i.e., met all inclusion/exclusion criteria, randomized and

treated correctly, and adhered to study procedures). The primary statistical analysis was used to test non-inferiority of FS 4IU VH S/D compared to staples with respect to complete wound closure at Day 28 after surgery. To assess the non-inferiority of success rate in wound closure with FS 4IU VH S/D as compared to that with staples, a one-sided 97.5% confidence interval for the difference of correlated proportions was calculated. The non-inferiority margin was set at 10%. If the lower limit of the one-sided confidence interval of the difference in closure rate between FS 4IU VH S/D treated and staples sites was above zero, it was considered to have been proven that FS 4IU VH S/D treatment is superior to grafting with staples in terms of statistical significance at the 0.025 alpha level ($p < 0.025$).

Median, 95% confidence interval of the median and range (or N, proportions and 95% confidence interval) are presented in tables of summary statistics for the secondary endpoints. Secondary endpoints measured by planimetry (% areas of hematoma/seroma, % area of engraftment, % area of wound closure) were analyzed twice: once without the re-grafted subjects and subjects who received additional staples, and once with the re-grafted sites and sites that received additional staples imputed to a 'worst case' result.

The purpose of the 2 analyses was to investigate the robustness of the endpoints. These variables were to be analyzed by paired t-test or non-parametric signed rank statistics if the data could not be normalized. All subjects receiving FS 4 IU VH S/D were included in the safety analysis. Probability of occurrence and 95% confidence interval of the probability of occurrence of AEs possibly or probably related to FS 4 IU VH S/D was calculated. Occurrence of local AEs is tabulated for FS 4IU VH S/D and staples separately. In agreement with the assessment of the primary efficacy endpoint, a 95% confidence interval was carried out for the difference of local AEs between FS 4 IU VH S/D and the control. The number, proportion and 95% confidence interval of the proportions are presented for categories of local AEs.

All AEs are presented in incidence tables by MedDRA type and body system. Experiences classified as possibly related or probably related to the FS 4 IU VH S/D administration are presented separately and combined with all other experiences.

Frequency and percent of subjects with serious adverse experiences are also displayed. All AEs, vital signs and concomitant medications data are provided in individual subject listings.

Schedule of Study Assessments

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study Procedures	Screening	Intra-Operative	Postoperative							
	Admission	Day 0	Day 1	Day 5	Day 14	Day 28	Mo 3	Mo 6	Mo 9	Mo 12
Informed Consent	X									
Inclusion/Exclusion	X									
Medical History/Acute Burn History	X									
Physical Exam	X									
Vital Signs		X ^a								
Randomization		X								
Record Number of Staples/ Volume FS 4IU VH S/D Applied		X								
Expression of Hematoma/Seroma			X							
Staple Removal				X						
Concomitant Medications	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^c	X ^c	X ^c	X ^c
Adverse Experiences	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^c	X ^c	X ^c	X ^c
Clinical Assessment										
Assessment of Hematoma/Seroma			X ^{d,e}							
Assessment of Engraftment				X ^f						
Assessment of Complete Wound Closure					X ^g	X ^g				
Investigator Assessment of Humanistic Outcomes		X		X	X	X				X

Study Procedures	Screening	Intra-Operative	Postoperative							
	Admission	Day 0	Day 1	Day 5	Day 14	Day 28	Mo 3	Mo 6	Mo 9	Mo 12
<i>Continued</i>										
Subject Assessment of Humanistic Outcomes				X	X	X				X
Global Photography		X	X	X	X	X	X	X	X	X
Day 28 Photographs for Blinded Review						X				
Vancouver Scar Scale							X ^h	X ^h	X ^h	X ^{h,i}
Clinical Laboratory Tests										
Urine/Serum pregnancy test	X									

^a Intraoperative time points include up to 30 min prior, 15±5 min, and 45±15 min.

^b Record all AEs/SAEs and concomitant medications for 28 days postoperative.

^c Record only SAEs and concomitant medications for SAEs.

^d Trace perimeter and hematoma/seroma(s), as necessary.

^e Trace perimeters of each test site separately.

^f Trace perimeter and areas of questionable viability, as necessary.

^g Trace perimeter and areas of loss, as necessary.

^h Assessment completed by blinded evaluator.

ⁱ Assess presence of keloids.

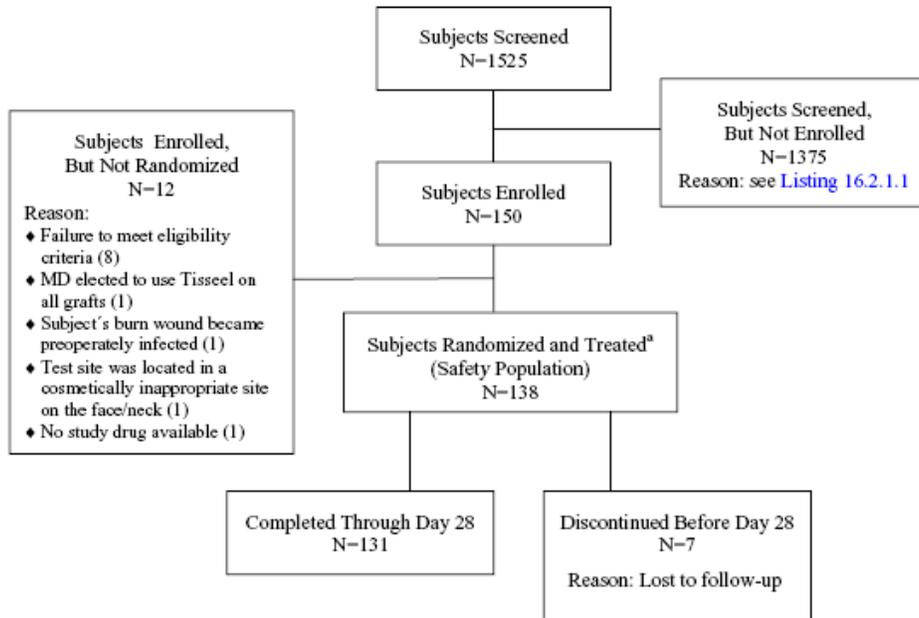
Results:

Study Population

A total of 138 subjects were randomized and treated at 13 study sites. The number of subjects randomized at each site ranged from 3 to 22. One thousand five hundred twenty-five burn patients were screened for eligibility. Of the 1525 patients screened, 150 were enrolled (signed consent) into the study. There were 1375 screen failures. In addition to the screen failures there were 12 subjects who were enrolled but not randomized due to 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, there were 138 of the 150 enrolled subjects randomized. All 138 subjects were treated at one test site with FS 4 IU VH S/D and a separate test site with staples.

Of the 138 randomized and treated subjects, 131 completed the Day 28 visit and 7 subjects were lost to follow-up prior to the Day 28 visit.

Table 14.1.2: Flowchart – Subject Disposition



^a. The number of randomized subjects is equal to the number of treated subjects.

Protocol Deviations:

Major protocol deviations:

Four subjects were excluded from the PP population due to major protocol violations. Subject 060001 had one contiguous piece of skin used to cover both test sites (FS 4IU VH S/D and staples), and was therefore excluded. Steri-strips were used at the control test site instead of the protocol-specified staples in Subject 060006. Staples used as temporary anchors at the FS 4IU VH S/D-treated site were not removed prior to placement of dressings in Subject 080003. Subject 080012 did not have staples placed parallel to the graft seam as stipulated in the protocol. The following table lists the summary of protocol deviations by site. Most deviations were related to not following the protocol schedule (e.g. taking photographs at scheduled time points or missing scheduled visits).

Table 14.1.5: Summary of Protocol Deviations by Site

Site Number	Number Subjects Enrolled	Protocol Deviation Category					Total
		Protocol Schedule	Eligibility	Study Drug Administration/ Technique	Other	Randomization	
01	17	8 : 5 (29.4%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	8 : 5 (29.4%)
03	17	12 : 8 (47.1%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	12 : 8 (47.1%)
04	19	10 : 7 (36.8%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	10 : 7 (36.8%)
06	10	4 : 3 (30.0%)	0 : 0 (0.0%)	7 : 5 (50.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	11 : 7 (70.0%)
07	12	9 : 7 (58.3%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	9 : 7 (58.3%)
08	13	4 : 4 (30.8%)	2 : 2 (15.4%)	2 : 2 (15.4%)	1 : 1 (7.7%)	1 : 1 (7.7%)	10 : 6 (46.2%)
09	4	2 : 2 (50.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	2 : 2 (50.0%)
10	10	10 : 4 (40.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	1 : 1 (10.0%)	1 : 1 (10.0%)	12 : 6 (60.0%)
11	5	2 : 2 (40.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	3 : 1 (20.0%)	0 : 0 (0.0%)	5 : 2 (40.0%)
13	23	25 : 15 (65.2%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	1 : 1 (4.3%)	26 : 15 (65.2%)
14	5	1 : 1 (20.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	1 : 1 (20.0%)
16	8	7 : 4 (50.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	0 : 0 (0.0%)	7 : 4 (50.0%)
Total	150	94 : 62 (41.3%)	2 : 2 (1.3%)	9 : 7 (4.7%)	5 : 3 (2.0%)	3 : 3 (2.0%)	113 : 70 (46.7%)

Primary Efficacy Analysis:

The ITT population consisted of all subjects with at least one available primary endpoint assessment. The wound closure assessment was analyzed as treated.

The sponsor defined the per protocol population (PP) as a subset of the ITT population: those meeting all inclusion /exclusion criteria, those who were randomized and treated correctly, no major protocol violations and had available valid assessments of wound closure by day 28 (subjects with completely missing pictures at one site were excluded from the PP population; if more than one reviewer assessed one site as not fully depicted or unassessable, the subject was excluded from the PP population); and those who had no open wound areas or excoriations due to a secondary cause in any test site by Day 28.

The intent-to-treat (ITT) population included 127 of the treated subjects. The 11 treated subjects not included in the ITT population were excluded for one of the following reasons: no primary endpoint assessment at both test sites; lost to follow-up prior to Day 28; or photographs not taken at both test sites on Day 28. The per protocol (PP) population consisted of the 106 subjects who met the criteria defined for the PP population in the *a priori* statistical analysis plan.

Table 14.2.17: Summary of Complete Wound Closure on Day 28 (Primary Efficacy Endpoint) / Intent-to-Treat

Complete Wound Closure on Day 28 ^a		
FS 4IU VH S/D [n of N (%)]	Staples [n of N (%)]	Lower Limit of 97.5% CI for FS 4IU VH S/D-Staples ^b
55 of 127 (43.3%)	47 of 127 (37.0%)	-0.029

^a Data is from independent panel review.

^b The lower limit of the 97.5% CI has to be greater than -0.1 to show non-inferiority.

Tabular Summary of Secondary Efficacy Analyses

**Table 14.2.43: Summary of Secondary Efficacy Endpoints - Continuous Variables
(Without Re-grafted Subjects and Without Subjects Who Received Additional Staples) / Intent-to-Treat**

	FS 4IU VH S/D					Staples					p-value (Signed Rank)
	N ^a	Mean	Median	95% CI for Median	Range	N ^a	Mean	Median	95% CI for Median	Range	
Percent Area of Hematoma/Seroma on Day 1	117	0.7	0.0	0.0 to 0.0	0.0 to 15.8	117	4.6	1.2	0.0 to 2.1	0.0 to 48.9	<.0001
Percent Area of Engraftment on Day 5	118	97.5	100.0	100.0 to 100.0	34.4 to 100.0	118	96.5	100.0	99.7 to 100.0	56.3 to 100.0	0.0250
Percent Area of Wound Closure on Day 14	113	96.9	100.0	99.6 to 100.0	68.5 to 100.0	112	95.8	99.8	98.4 to 100.0	62.7 to 100.0	0.0570
Percent Area of Wound Closure on Day 28	114	98.8	100.0	100.0 to 100.0	74.2 to 100.0	114	98.1	100.0	100.0 to 100.0	78.1 to 100.0	0.0132

^a Subjects with unavailable status regarding re-grafting (no data of investigator's assessment of complete wound closure by Day 28) were excluded from the calculations of the continuous secondary endpoints.

**Table 14.2.44: Summary of Secondary Efficacy Endpoints - Continuous Variables
(With Re-grafted Subjects and With Subjects Who Received Additional Staples) / Intent-to-Treat**

	FS 4IU VH S/D					Staples					p-value (Signed Rank)
	N ^a	Mean	Median	95% CI for Median	Range	N ^a	Mean	Median	95% CI for Median	Range	
Percent Area of Hematoma/Seroma on Day 1	129	6.9	0.0	0.0 to 0.0	0.0 to 100.0	129	10.7	1.6	0.5 to 2.7	0.0 to 100.0	<.0001
Percent Area of Engraftment on Day 5	130	91.3	100.0	100.0 to 100.0	0.0 to 100.0	130	90.6	100.0	98.8 to 100.0	0.0 to 100.0	0.0684
Percent Area of Wound Closure on Day 14	125	90.5	100.0	99.4 to 100.0	0.0 to 100.0	124	89.6	99.3	97.7 to 100.0	0.0 to 100.0	0.1092
Percent Area of Wound Closure on Day 28	125	92.4	100.0	100.0 to 100.0	0.0 to 100.0	126	91.9	100.0	100.0 to 100.0	0.0 to 100.0	0.0950

^a Subjects with unavailable status regarding re-grafting (no data of investigator's assessment of complete wound closure by Day 28) were excluded from the calculations of the continuous secondary endpoints.

Table 14.2.47: Number of Subjects who Required Expression of Hematoma/Seroma / Intent-to-Treat

	FS 4IU VH S/D [n of N (%)]	Staples [n of N (%)]
Expression of Hematoma / Seroma Required - Day 1	31 of 127 (24.4%)	72 of 127 (56.7%)
Expression of Hematoma / Seroma Required - Day 2	10 of 127 (7.9%)	13 of 127 (10.2%)

Table 14.2.60: Summary of Complete Wound Closure on Day 28 (Primary Efficacy Endpoint) by Test Site Location / Intent-to-Treat

Location	Complete Wound Closure on Day 28	
	FS 4IU VH S/D [n of N (%)]	Staples [n of N (%)]
Extremities	41 of 110 (37.3%)	39 of 111 (35.1%)
Neck and Torso	14 of 17 (82.4%)	8 of 16 (50.0%)

Table 14.2.62: Summary of Complete Wound Closure on Day 28 (Primary Efficacy Endpoint) by Dosing Volume / Intent-to-Treat

Dosing Volume Applied [(mL/cm ²)*100]	Wound Closure for FS 4IU VH S/D [n of N (%)]
< 2	35 of 81 (43.2%)
2 - 4	17 of 36 (47.2%)
> 4	2 of 6 (33.3%)

Table 14.2- 8 Summary of Adherence of FS 4IU

Endpoint	FS 4IU [n/N (%)]
Adherence of FS 4IU on Day 0	
EXCELLENT	33/ 40 (82.5 %)
GOOD	6/ 40 (15.0 %)
FAIR	1/ 40 (2.5 %)
POOR	0/40 (0.0 %)

Safety

Deaths

There were no deaths during Part A of the study.

Protocol defined Serious Adverse Events

1. Incidence of SAEs occurring at test sites

There were 3 incidences of infection and 1 incidence of staphylococcal infection occurring at both the FS 4IU VH S/D test site and the stapled test site (Subject 010005, Subject 040011, Subject 040016, and Subject 100010). There were 4 incidences of skin graft failure occurring at the FS 4IU VH S/D test site (Subject 040011, Subject 040016, Subject 110003, and Subject 160008) and 3 incidences at the stapled site (Subject 040011, Subject 040016, and Subject 110003).

2. Incidence of SAEs not occurring at test sites

There were 2 incidences of infections (Subject 160005, and Subject

130010), 1 incidence of staphylococcal infection (Subject 010005), 3 incidences of skin graft failure (Subject 040015, Subject 100010, and Subject 160007), 1 incidence of acute respiratory distress (Subject 130017), and 1 incidence of excessive granulation tissue (Subject 060003).

3. Incidence of non-serious AEs occurring at test sites (as defined by protocol)

At FS 4IU VH S/D test sites, there were 35 incidences of skin graft failure, 29 incidences of pruritus, 4 incidences of infection, 2 incidences of graft complication, 2 incidences of dermal cyst, 2 incidences of excessive granulation tissue, and a single incidence of each of the following: edema peripheral, excoriation, culture wound, joint contracture, skin maceration, and hematoma. Five of the 35 incidences of skin graft failure, 2 of the 29 incidences of pruritus, and 1 of the 2 incidences of dermal cyst were considered related to FS 4IU VH S/D. A similar incidence of non-serious AEs occurred at 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. Of the 15 incidences of graft complication at the stapled site, 12 of them were due to retained staples after the Day 5 visit

Reviewer Tabulation of All Adverse events at test sites

	ARTISS	STAPLES
<u>Deaths</u>	0	0
<u>General</u>		
Peripheral edema	1	1
<u>Infections and infestations</u>		
Infection (NOS)*	6	7
Staph infection	1	1

N.B. *Not otherwise specified

Injury, poisoning, And procedural complications

Graft complication (Including retained staples)	2	14
Skin graft failure	35	32
Hematoma	1	2
Seroma	0	1

Investigations

Wound culture	1	1
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Musculoskeletal and

Connective tissue disorders

Joint contracture	1	1
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**Skin and subcutaneous
Tissue disorders**

Decubitus ulcer	0	1
Dermal cyst	2	3
Excoriation	1	2
Excessive granulation tissue	2	1
Pruritus	28	29
Skin maceration	1	1

4. Incidence of non-serious AEs not occurring at test sites

There was a higher rate of graft complication in stapled test sites (10.1%) compared with FS 4 IU VH S/D test sites (1.4%). The rates of skin graft failure were similar between FS 4 IU VH S/D test sites (25.4%) and stapled test sites (23.2%).

Table 14.3.21: Specific Symptoms of Adverse Experiences at Test Sites

System Organ Class / Preferred Term	FS 4IU VH S/D			Staples		
	# Subjects	Proportion	95% Exact CI for Proportion	# Subjects	Proportion	95% Exact CI for Proportion
General disorders and administration site conditions						
Oedema peripheral	1	0.7%	0.0% to 4.0%	1	0.7%	0.0% to 4.0%
Infections and infestations						
Infection	6	4.3%	1.6% to 9.2%	7	5.1%	2.1% to 10.2%
Staphylococcal infection	1	0.7%	0.0% to 4.0%	1	0.7%	0.0% to 4.0%
Injury, poisoning and procedural complications						
Excoriation	1	0.7%	0.0% to 4.0%	2	1.4%	0.2% to 5.1%
Graft complication	2	1.4%	0.2% to 5.1%	14	10.1%	5.7% to 16.4%
Seroma	0	0.0%	0.0% to 2.6%	1	0.7%	0.0% to 4.0%
Skin graft failure	35	25.4%	18.3% to 33.5%	32	23.2%	16.4% to 31.1%
Investigations						
Culture wound	1	0.7%	0.0% to 4.0%	1	0.7%	0.0% to 4.0%
Musculoskeletal and connective tissue disorders						
Joint contracture	1	0.7%	0.0% to 4.0%	1	0.7%	0.0% to 4.0%
Skin and subcutaneous tissue disorders						

Table 14.3.21: Specific Symptoms of Adverse Experiences at Test Sites

System Organ Class / Preferred Term	FS 4IU VH S/D			Staples		
	# Subjects	Proportion	95% Exact CI for Proportion	# Subjects	Proportion	95% Exact CI for Proportion
Decubitus ulcer	0	0.0%	0.0% to 2.6%	1	0.7%	0.0% to 4.0%
Dermal cyst	2	1.4%	0.2% to 5.1%	3	2.2%	0.5% to 6.2%
Excessive granulation tissue	2	1.4%	0.2% to 5.1%	1	0.7%	0.0% to 4.0%
Pruritus	28	20.3%	13.9% to 28.0%	29	21.0%	14.5% to 28.8%
Skin maceration	1	0.7%	0.0% to 4.0%	1	0.7%	0.0% to 4.0%
Vascular disorders						
Haematoma	1	0.7%	0.0% to 4.0%	2	1.4%	0.2% to 5.1%

Reviewer tabulation of All Adverse events at Non test sites

<u>Deaths</u>	0
<u>General</u>	
Chills	6
Inflammation	1
Infusion site reaction	2
Generalized edema	2
Peripheral edema	2
Pyrexia	12
<u>Blood and Lymphatic System disorders</u>	
Lymphadenopathy	1
Thrombocythemia	2
<u>Cardiac disorders</u>	
Tachycardia	6
Ventricular extrasystoles	1
Hypotension	2
Hypertension	8
<u>Eye disorders</u>	
Conjunctivitis	1
<u>Ears, Nose</u>	
Otitis externa	1
Otitis media	1
Rhinitis	1
Tympanic membrane perforation	1
<u>Gastrointestinal</u>	

Abdominal distention	1
Constipation	34
Diarrhea	2
Dyspepsia	1
Flatulence	1
Hemorrhage	1
GERD	1
Hematochezia	1
Nausea	11
Vomiting	4
Pharyngitis (streptococcal)	1

Infections and infestations

Abscess	1
Bacteremia	1
Bacteria infection	1
Candidiasis	3
Cellulitis	2
Central line infection	1
Enterobacter sepsis	1
Herpes infection	1
Infection (NOS)	11
Staph infection	1
Urinary tract infection	3
Vulvovaginal mycotic infection	2

**Injury, poisoning,
And procedural complications**

Graft complication	2
Skin graft failure	9
Donor site complication	4
Fall	1
Hematoma	3
Seroma	1

Investigations

Wound culture	2
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Laboratory

Hemoglobin decreased	12
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Metabolism and nutrition

Decreased appetite	1
Dehydration	1

Fluid overload	1
Hyperglycemia	6
Hyperkalemia	2
Hypermagnesemia	1
Hypochloremia	1
Hypocalcemia	3
Hypoglycemia	1
Hyponatremia	4
Hypomagnesemia	3
Hypophosphatemia	1
Malnutrition	
Metabolic acidosis	
Respiratory acidosis	

**Musculoskeletal and
Connective tissue disorders**

Joint contracture	1
Muscle spasms	1
Musculoskeletal stiffness	1

Nervous system

Headache	1
Parkinsonism	1
Sedation	1

Psychiatric

Agitation	4
Anxiety	6
Confusion	1
Depression	1
Hallucination	2
Insomnia	16
Post traumatic stress disorder	1

Renal and urinary disorders

Bladder spasm	1
Incontinence	1

RESPIRATORY

Cough	1
Hypoxia	1
Laryngeal edema	1

Pharyngolaryngeal pain	5
Pneumonia	2
Pulmonary edema	1
Respiratory depression	1
Stridor	1
Wheezing	1

Skin and subcutaneous

Tissue disorders

Contact dermatitis	1
Decubitus ulcer	2
Dermal cyst	2
Erythema	1
Excessive granulation tissue	2
Pruritus	45
Rash	10
Skin disorder	1

IV. Pediatric Research Equity Act (PREA)

Pediatric patients were studied in both the phase 1 / 2 study and the pivotal study. The primary efficacy analysis for pediatric patients is depicted in summary form in the following table:

Table 14.2.23: Summary of Complete Wound Closure on Day 28 (Primary Efficacy Endpoint) by Age / Intent-to-Treat

Age	Complete Wound Closure on Day 28	
	FS 4IU VH S/D [n of N (%)]	Staples [n of N (%)]
<=6 years	13 of 18 (72.2%)	13 of 18 (72.2%)
7-18 years	6 of 19 (31.6%)	5 of 19 (26.3%)
>18 years	36 of 90 (40.0%)	29 of 90 (32.2%)

The rate of complete wound closure by day 28 was higher in the less than or equal to 6 years of age group for FS 4 IU VH S/D (72.2%) compared to ages 7-18 , in which the closure rate by day 28 was 31.6%.

Redefining the age groups as less than or equal to 18 (N=37) and greater than 18 (N=90), the difference between the two groups for wound closure by day 28 is less striking. Nonetheless the younger age group appeared to close wounds better. This analysis is shown in the following table:

Table 14.2.24: Summary of Complete Wound Closure on Day 28 (Primary Efficacy Endpoint) by Age / Intent-to-Treat

Age	Complete Wound Closure on Day 28	
	FS 4IU VH S/D [n of N (%)]	Staples [n of N (%)]
≤18 years	19 of 37 (51.4%)	18 of 37 (48.6%)
>18 years	36 of 90 (40.0%)	29 of 90 (32.2%)

Overall, the efficacy of FS 4IU VH S/D was demonstrated in subjects < 18 years old; 72.2% of the ≤ 6 years old group (N=18) and 31.6% of the 7-18 years old group (N=19) achieved complete wound closure by Day 28 (ITT).

V. FDAAA Pediatric Review requirements:

The summary of the clinical studies and pediatric rule requirements were presented to the Pediatric Review Committee on January 30, 2008. The recommendations from the panel were that the 0-1 year of age group be waived because there are too few patients in this age group to be studied or that safety and efficacy of Artiss be extrapolated to this age group. It is my recommendation that the 0-1 year of age group be waived. I cannot be certain that the immature coagulation system of an infant would not be adversely affected by application of Artiss. It is also unlikely that the sponsor will be able to conduct a substantive post marketing study targeting the 0 to 1 year old age group for the burn grafting indication.

VI. Financial Disclosure:

In item 19 of the original BLA submission regarding Certification: Financial Interests and Arrangements of Clinical Investigators, the sponsor has checked the following as true:

“As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I also certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

VII. Reviewer comments/ final recommendations:

It was noted during the mid-cycle review that the sponsor had not submitted all CRF’s for this study. At the mid-cycle FDA requested that all CRFs for studies 550002 and 550201 be submitted to the BLA. The sponsor complied with this request.

The sponsor met the pre-specified primary endpoint. FS 4IU VH S/D appears to be at least as effective as staples for adhering autologous skin grafts to surgically prepared burn wound beds in pediatric and adult patients. Overall, the use of FS 4IU for adhering autologous grafts to surgically prepared burn wound bed sites appears to be at least as safe as staples for the same purpose.

This reviewer recommends approval of Artiss for graft adherence. The sponsor has indicated in a submitted Summary Basis of Approval that they have a -----

claim. Although complete wound closure was the primary endpoint in the pivotal trial, it should be noted that the burn wound beds were covered with autologous sheet graft material for coverage of the wound. The application of Artiss **facilitates** wound closure. I think it is important to make this distinction. Therefore, I recommend that Artiss be approved for burn graft adherence and facilitation of wound closure.

VIII. Labeling Review:

A final labeling review memo (to include recommendations from the Advertising, Promotion and Labeling Branch) is appended below.



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: January 30, 2008

FROM: Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch,
Division of Hematology, OBRR

SUBJECT: STN 125266, FS 4IU VH S/D, (Artiss) Labeling Review (Final)

SPONSOR: Baxter Healthcare

THROUGH: Toby Silverman, MD, Chief, Clinical Review Branch

TO: File

Cc: Jean Makie
Lisa Stockbridge

Clinical Trial Summary:

In a prospective, randomized, controlled, multi-center clinical study, FS 4 IU VH S/D (Artiss) was investigated for non-inferiority to staples for the fixation of split thickness skin grafts in burn patients. The study population consisted of 138 patients. Each patient served as his/her own control. In each patient, two comparable test sites were identified. On one test site the skin graft was fixed with staples (control) and the other test site was

fixed with Artiss. The primary endpoint was wound closure (defined as full coverage of the wound with a contiguous layer of viable epithelium) at day 28.

Artiss was demonstrated to be non-inferior to staples for graft fixation and complete wound closure at day 28.

Pediatric Review Committee Recommendations:

The Artiss package insert was presented to the Pediatric Review Committee on January 30, 2008. The committee recommended either a waiver of the pediatric portion because 1.) there would be too few patients to study in the less than 1 year old age group for this indication or 2.) the division could make the determination that the efficacy and safety of Artiss could be extrapolated to the pediatric population (to include infants – i.e. ages 2 and under). This reviewer believes that the efficacy and safety information for ages one year and less should be waived since grating procedures for this age group are not common. This memo includes the following:

1. Clinical trial summary
2. Clinical Reviewer labeling recommendations
3. Appendix 1: Baxter's proposed labeling for Artiss
4. Appendix 2: APLB review memo dated January 29, 2008

Recommendations for the **HIGHLIGHTS SECTION**

General

1. Please submit labeling in 8 font or greater. You may not use the specific font type called Arial narrow.

Drug Names

2. Please include the proprietary name and proper names of the biological product.
3. For biologic products, the dosage form and route of administration must be on the line underneath the proper name since the proper name does not include the drug's dosage form or route of administration. See 21 CFR 600.3 (k) and Section 351 of the PHS Act.
4. Please add "for topical use only" to the established name.

Indications and Usage

5. Major limitations of use must be briefly noted in this subsection. Please add the following statement: "Artiss is not indicated for hemostasis (1)." You proposed a similar statement under Sections 2 and 5.3 of the Full Prescribing Information (FPI). Please delete the statement from these sections and add it to section 1 of the FPI.

Dosage and Administration

6. Please add information regarding the recommended dosage regimen, starting dose, or dose range. (Reference Full Prescribing Information section 2).
7. No information is provided regarding the use of ARTISS (Freeze-dried) within four hours of reconstitution. Please add this information.
8. We note that Easyspray is a trademark of Baxter. This device does not appear to be the only one available for use with ARTISS (see Full Prescribing Information,

- section 2.3). The statement can be used to market and promote Baxter's Easyspray device. Please revise the information in the HIGHLIGHTS section to state only generalized spray device information.
9. Please add the following as the first bullet to this section: "For Topical Use Only. Do Not Inject. Apply on surface of prepared wound beds only. (bolded)"
 10. Please make the following the last bullet in this section: "Vials are for single use only. Discard unused contents."

Contraindications

11. Please delete "Injection directly into blood vessels" since this information relates to Dosage and Administration and should be located in that subsection of the Highlights (as well as the Dosage and Administration section of the Full Prescribing Information).

Warnings and Precautions

12. The bullet, "Made from human plasma" should include the potential consequence that makes this a precaution. For example, the bullet could be revised to state: "This product is made from pooled human plasma which may, theoretically, contain infectious agents."
13. The adverse reactions section should list the most common adverse reactions along with the inclusion criteria. The statement that there were less than 1/100,000 reports of allergic/anaphylactic reactions occurring from use of ARTISS is misleading because it does not reflect the adverse reactions reported in the clinical trials and because the denominator implies a much wider experience with Artiss than has occurred in its clinical development. Accordingly, please revise this section to be consistent with the adverse reactions seen in the clinical trials for Artiss. For example, "Adverse reactions occurring in greater than 1% of patients treated with Artiss were skin graft failure and pruritus."
14. Anaphylactic reactions are a serious adverse event that is addressed in the warnings section of the FPI. Therefore, it does not need to be included in this subsection.

Drug Interactions

15. The statement "None known" minimizes the fact that no drug interaction studies have been performed. This heading is optional and should be omitted from the Highlights section for Artiss.

Use in Specific Populations

16. This subsection is reserved for the discussion of clinically important differences in response on specific populations. The pregnancy category should not be included in this subsection of the Highlights and should be deleted.
17. Use in Specific Populations is an optional heading and should be omitted from the Highlights section for Artiss.

18. Please revise the heading – **FULL PRESCRIBING INFORMATION** –so that it appears at the beginning of the FPI in upper-case letters and bold type.
19. Please ensure that no page header or footer appears in the final FPI document. They now appear in the sponsor’s proposed draft (PDF version).

INDICATIONS AND USAGE

20. To highlight its importance, APLB recommends moving the limitation of use statement, “Artiss is not indicated for hemostasis,” to this section from the Dosage and Administration section.

DOSAGE AND ADMINISTRATION

21. Please move the statement, “Artiss is not indicated for hemostasis” to the Indications and Usage section. (See comment above).
22. Please delete “listed in the following table” (line 9) to be consistent with language used in subsequent subsections.

2.1 Preparation of ARTISS Kit (Freeze-Dried)

23. Precautionary statements are scattered throughout Section 2.1. To ensure the safe use of ARTISS (Freeze Dried), we recommend that these statements be prominently displayed together prior to the preparation information.
24. To ensure the safe use of ARTISS (Freeze Dried) in the surgical setting, please delete the sentence, “If a FIBRINOTHERM is not available, contact Baxter...” and replace it with instructions for reconstitution using a water bath or incubator [see those provided for ARTISS (Frozen)].
25. Information provided under “Preparation of Sealer Protein Solution” and “Preparation of Thrombin Solution” is specific to the use of the Fibrinotherm device. Therefore, please revise the subheadings to include “with FIBRINOTHERM.”
26. The placement of information pertaining to the Fibrinotherm device in section 2.1 detracts from the general preparation information for ARTISS (Freeze Dried). Please move this information to “Preparation of Sealer Protein Solution with FIBRINOTHERM.”
27. Please delete the last paragraph in section 2.1 regarding the Fibrinotherm device and insert it as step 1 under “Preparation of Sealer Protein Solution with FIBRINOTHERM” to ensure that it is used appropriately and does not deter from the safe preparation and administration of ARTISS.
28. Under the preparation of solution subsections, the statement “Do not use iodine-containing preparations such as betadine for disinfection” does not provide adequate safety information regarding denaturing by alcohol or heavy metal ions (see section 5.3). Please revise these precautionary statements appropriately to ensure the safe use of ARTISS.

2.2 Preparation of ARTISS Prefilled Syringe (Frozen)

29. Precautionary statements are scattered throughout Section 2.2. To ensure the safe use of ARTISS (Frozen), we recommend that they be prominently displayed together before the detailed preparation information.
30. Please delete the numbers preceding the thawing instructions because they imply sequential steps when the information is unique to each method.

2.3 Method of Application

31. Please delete “Easyspray and Spray Set” because they promote the use of a device that is manufactured by the sponsor, but not provided with Artiss packaging.
32. No instructions are provided on how to attach the DUPLOJECT or DUO system to the spray device. To ensure the safe administration of ARTISS, please add general instructions under an “Instructions for Use” section or a statement referring to the spray device’s package instructions.
33. In sentence two, paragraph two, is the omission of “normal” (e.g., normal saline) before saline an oversight?
34. In sentence two, paragraph four, we recommend the addition of “final” to clarify strength of solidified sealant at the end of two hours. Also, is it important for the surgeon to know that ARTISS reaches 70% of its strength in 10 minutes vs. any other time elapse and strength achieved? If this information is critical to the safe application of ARTISS, we suggest the use of a table to display relevant solid sealant strengths and set time elapse. Otherwise, the parenthetical statement may be used promotionally.
35. You reference the instructions for use provided with the DUPLOJECT system (a copy was provided by sponsor with submission). The DUO set will be included with ARTISS (Frozen) packaging, but only brief instructions are provided in comparison to the detailed package insert for DUPLOJECT. Please provide comparable instructions for DUO set to be included with ARTISS (Frozen) under an “Instructions for Use” section to ensure the safe administration of the product.

4 CONTRAINDICATIONS

4.2 Aprotinin Hypersensitivity

36. Please revise this contraindication to utilize command language: “Do not use Artiss in individuals with a known hypersensitivity to aprotinin.”
37. please include details specific to the hypersensitivity with aprotinin with the contraindication rather than cross-reference to the Warnings and Precautions section.

5 WARNINGS AND PRECAUTIONS

38. Items in this section should be listed in order of importance. Theoretical risks (e.g., viral transmission) should be listed last. Please note that the Warnings and

Precautions subsection of the Highlights section should reflect the order in this section.

5.1 Infection Risk from Human Plasma

39. You propose details of viral removal that minimize that fact that there is a risk of viral infection with Artiss. The cross-referencing is unnecessary and serves to further minimize the important message. Suggested wording for this section can be found in *Guidance for Industry: Revised Preventative Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products*. We recommend the following wording for this section: “This product is a derivative of human plasma. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered remote. No cases of transmission of viral diseases or CJD have been identified for Artiss.”
40. The Baxter telephone number does not belong in this section. Suspected viral transmission should be reported to a dedicated company phone line or Medwatch. These numbers are the ones provided in the Highlights section of the FPI.
41. Please move the further instruction to physicians regarding the use in pregnant patients to the Pregnancy subsection of the Use in Specific Populations section.
42. Further instruction to physicians regarding patient counseling belongs in the Patient Counseling section (Section 17).
43. The use in immunocompromised patients appears to be cross-referenced to the Pregnancy subsection of the Special Populations section. If this was your intent, please comment.

5.2 Hypersensitivity/Allergic/Anaphylactic Reactions

44. In sentence one, paragraph one, please delete the phrase, “As with other protein products” because it minimizes the importance of known reactions related to ARTISS.
45. In sentence two, paragraph one, it is unclear that this incidence rate (< 1/100,000 cases) is only from the use of ARTISS, Baxter’s other fibrin sealant (Tisseel), or all other marketed fibrin sealants worldwide or U.S. alone. Additionally, it is unclear if these “cases” are only from clinical trials of ARTISS. Please verify this information.
46. Please delete the term “isolated” because it is vague and can be misleading.
47. In sentence three, paragraph one, we recommend that the broad reference to “fibrin sealant preparation containing aprotinin” be replaced with “ARTISS.”

5.3 Application Precautions

48. Please delete the statement, “Artiss is not intended for promoting hemostasis of the donor sight.”

49. In sentence one, paragraph two, please use command language.
50. To ensure the safe application of ARTISS, we suggest adding “and made as dry as possible” to sentence two, paragraph three.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions

51. This section must describe the overall adverse reaction profile based on the entire safety database for Artiss. Adverse reactions must be listed in decreasing order of frequency. As stated above, the most common adverse reactions appear to be graft failure and pruritus.
52. If applicable, adverse reactions suspected in the product class may be included. In this case, the class adverse reaction is potentially fatal and should be listed here and cross-referenced the hypersensitivity to the Warnings and Precautions.

6.2 Clinical Trials Experience

53. The limitations of clinical trial reporting of adverse reactions (lines 252-253) must precede the presentation of adverse reactions for the clinical trials.
54. Please use the term, “adverse reactions” instead of the abbreviations “ADR” or “AEs” and the term “adverse events.”
55. Because minimal adverse events were observed in the clinical trial, please consider combining the first two paragraphs to provide more concise safety information.
56. The statement, “None of the events were classified as serious” should be deleted because a.) it is redundant with the reporting of “non-serious adverse events” and b.) because its placement minimizes the reported adverse reactions that succeed it.
57. Please appropriately cite tables containing clinical data in the text and label the tables accordingly.
58. Please remove “System Organ Class” from the table of adverse reactions because it is unnecessary due to the brevity of the table.

6.3 Post Marketing

59. Baxter markets only Tisseel so please revise “Sealants” to sealant (i.e. singular). Also, please do not capitalize “Fibrin Sealant” because it can be mistaken for a proprietary name.

7 DRUG INTERACTIONS

60. Please delete “formal”, since it is vague. Baxter either conducted drug interaction studies or did not. Please comment.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

61. Please replace the phrase “clearly needed” with “deemed medically necessary” in the last sentence.
62. Please consider the addition of wording regarding the Parvovirus precaution to this section since the precaution is specifically directed at pregnant women.

8.4 Pediatric Use

63. You did not study pediatric patients less than 1 year of age in the clinical trials intended to support the burn grafting indication; therefore, please revise the sentence, “In a clinical trial, the efficacy and safety of ARTISS in pediatric patients was not different from an adult population” to “In a clinical trial, the efficacy and safety of ARTISS in pediatric patients (ages greater than 1 year of age to 16 years of age) was not different from an adult population. Additionally, the clinical data should be described in section 14, which currently does not describe any of the study populations.

11 DESCRIPTION

64. Please delete the sentence “Artiss is intended only for topical administration.” This information is stated in section 2.
65. Please delete “for available package sizes and presentations” from the last sentence. The reference to section 3 can stand alone.

12.2 Pharmacodynamics

66. Avoid using vague terms such as “most” in sentence two, paragraph two. The actual amount of thrombin that is adsorbed should be stated.

12.3 Pharmacokinetics

67. To improve clarity, please revise this section to state, “Pharmacokinetic studies were not conducted. Because ARTISS is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.”

12.4 Other Clinical Pharmacology Information

68. Please appropriately reference the table in the text and label it accordingly.

14. CLINICAL STUDIES

69. Please include a description of the overall clinical trial database including overall exposure (number of patients, dose, duration), demographics of exposed population, designs of trial, and any critical exclusions from safety database should be included. Currently, no study populations are described.
70. Please appropriately cite the table in the text and label it accordingly.
71. Given the actual number of patients in the clinical trial, the percentages provided in the table may be used promotionally and could be misleading. Please replace the table with statistical information in a text format.
72. Please delete lines 50-52 regarding the superiority claims of Artiss over staples for patient satisfaction and overall quality of healing fixation as judged by investigators since these are not objective validated endpoints and were studied as part of supplemental exploratory analyses.

16 HOW SUPPLIED/STORAGE AND HANDLING

73. In the sentence following the table, please delete “for contents” because it is not needed.
74. In the table, please add “with Duo Set” to ARTISS (Frozen) because the device is always supplied with this formulation.
75. Please delete the information under “Accessories.” It is promotional for your other products that are not provided in ARTISS packaging.

17 PATIENT COUNSELING INFORMATION

76. In Sentence one, “physicians” should be singular.
77. Please use command language: replace “encouraged” with “instructed” in sentence two.

Instruction for Use

78. Please see comments above regarding the inclusion of instructions for use for the DUO set and spray device.

Appendix 1: Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARTISS safely and effectively. See full prescribing information for ARTISS

ARTISS [Fibrin Sealant]
Initial U.S. Approval: xxxx

RECENT MAJOR CHANGES

INDICATIONS AND USAGE

ARTISS is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and pediatric populations (2)

DOSAGE AND ADMINISTRATION

ARTISS Kit (Freeze-Dried) requires reconstitution prior to use (3.1)
ARTISS (Frozen) requires thawing prior to use (3.2)

Apply ARTISS as a thin layer using the Easyspray and Spray Set (3.3, 6.3)

Store ARTISS Kit (Freeze-Dried) at 2-25°C. Avoid Freezing (16)
Store ARTISS (Frozen) at ≤ -20°C. Unopened pouches, thawed at room temperature, may be stored for up to 5 days at 15-25°C. The product must be used within 12 hours after warming to 33-37°C or removal from original pouches. Do not refrigerate or re-freeze (16)

DOSAGE FORMS AND STRENGTHS

ARTISS Kit (Freeze-Dried) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with and without the DUPLOJECT system (4.1)
ARTISS (Frozen) is supplied as a 10 mL (total volume) pack size with the DUO set (4.1)

CONTRAINDICATIONS

- Injection directly into blood vessels (5.1)
- Known hypersensitivity to aprotinin (5.2, 6.2, 7.1)

WARNINGS AND PRECAUTIONS

- Apply only as thin layer (3.3, 6.3)
- Use caution when applying ARTISS with pressurized gas (6.3)
- Made from pooled human plasma (6.1)
- Exposure to solutions containing alcohol, iodine or heavy metals may cause ARTISS to be denatured (6.3)

ADVERSE REACTIONS

There have been reports (< 1/100,000) of allergic/anaphylactic reactions from use of ARTISS (6.2, 7.1, 7.3)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

None known (8)

USE IN SPECIFIC POPULATIONS

Pregnancy Category C (9.1)

Pediatric

ARTISS was used in 35 pediatric patients aged 1.1 to 16 years to affix skin grafts to burn wounds. Nineteen of these patients were less than or equal to 6 years old. Efficacy and safety in these pediatric patients was not different from an adult population.

1.1 Geriatric Use

The

See 17 for PATIENT COUNSELING INFORMATION

Revised: xx/200x

COMPREHENSIVE PRESCRIBING INFORMATION: INDEX *

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14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

ARTISS (frozen and lyophilized) is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and pediatric populations.

2 DOSAGE AND ADMINISTRATION

**FOR TOPICAL USE ONLY – DO NOT INJECT.
ARTISS IS NOT INDICATED FOR HEMOSTASIS.**

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 are listed in the following table:

Approximate area requiring skin graft fixation	Required package size of ARTISS
100 cm ²	2 mL
200 cm ²	4 mL
500 cm ²	10 mL

2.1 Preparation of ARTISS Kit (Freeze-Dried)

ARTISS Kit contains the following substances in four separate vials:

- Sealer Protein Concentrate (Human)
- Fibrinolysis Inhibitor Solution (Synthetic)
- Thrombin (Human)
- Calcium Chloride Solution

Freeze-dried Sealer Protein Concentrate and Thrombin are reconstituted in Fibrinolysis Inhibitor Solution and Calcium Chloride Solution, respectively. The Sealer Protein Solution and Thrombin Solution are then combined using the DUPLOJECT Preparation and Application System, or an equivalent delivery device cleared by FDA for use with ARTISS to form the Fibrin Sealant.

Use separate syringes for reconstituting Sealer Protein and Thrombin solutions and for application to prevent premature clotting.

For ease of handling, the FIBRINOTHERM, a combined heating and stirring device, has been developed. The FIBRINOTHERM device maintains a constant temperature of 37°C and has been designed to hold the various vial sizes. Heating and stirring can be operated independently. If a FIBRINOTHERM device is not available, contact Baxter (1-800-423-2090) for assistance with reconstitution using a water bath or incubator.

After plugging the FIBRINOTHERM into an electrical socket and activating the warmer using the amber switch, place all four vials from the ARTISS kit into prewarmed warming wells with the appropriate sized adaptor ring. Refrigerated product may take up to 5 minutes to warm. Room temperature product will take less.

Preparation of Sealer Protein Solution

1. Ensure that the stirring mechanism of the FIBRINOTHERM device is initially switched off (green switch).
2. Remove the flip-off caps from the vial containing the Sealer Protein Concentrate and the vial containing the Fibrinolysis Inhibitor Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry. **Do not use iodine-containing preparations such as betadine for disinfection.**
3. Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein Concentrate using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with ARTISS (see directions provided with the device system for specific reconstitution instructions). Gently swirl the vial to ensure that the freeze-dried material is completely soaked.
4. Place the vial into the largest opening of the FIBRINOTHERM device with the appropriate adaptor. Switch on the stirrer (green switch) and allow the vial contents to stir until all Sealer Protein Concentrate is dissolved.
5. Reconstitution of the freeze-dried Sealer Protein Concentrate is complete as soon as no undissolved particles are visible. Otherwise, return the vial to the FIBRINOTHERM device and agitate for a few more minutes until the solution appears homogeneous.

Notes:

- Do not use the Sealer Protein Concentrate until it has fully dissolved. If the Sealer Protein Concentrate has not dissolved within 20 minutes using the FIBRINOTHERM device, discard the vial and prepare a fresh kit.
- If not used promptly, keep the Sealer Protein Solution at 37°C without stirring. To ensure homogeneity, switch on the stirrer of the FIBRINOTHERM device shortly before drawing up the solution.

Preparation of Thrombin Solution

1. Remove the flip-off caps from the vial containing Thrombin and the vial containing Calcium Chloride Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry. **Do not use iodine-containing preparations such as betadine for disinfection.**
2. Transfer the contents of the vial with Calcium Chloride Solution into the vial containing the freeze-dried Thrombin using the sterile reconstitution components provided with the DUPLOJECT Preparation and Application System, or an equivalent device cleared by FDA for use with ARTISS (see directions provided with the device system for specific reconstitution instructions).
3. Swirl briefly.
4. Place the vial into the adapted opening of the FIBRINOTHERM device.
5. Reconstitution of Thrombin is complete when all of the Thrombin concentrate is dissolved.
6. Keep the Thrombin Solution at 37°C until used.

Transferring to the Sterile Field

For transfer of the Sealer Protein Solution and the Thrombin Solution to the sterile field, the scrub nurse should withdraw the solutions while the circulating nurse holds the non-sterile vials. The solutions should be withdrawn slowly by firm constant aspiration to reduce the risk of large air bubbles.

After reconstitution, the product must be used within 4 hours.

**DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C.
DO NOT REFRIGERATE AFTER RECONSTITUTION.**

See *DOSAGE AND ADMINISTRATION, Method of Application (2.3)*.

2.2 Preparation of ARTISS Prefilled Syringe (Frozen)

ARTISS prefilled syringe (frozen) can be prepared (thawed) using one of two options:

1. Room Temperature Thawing

Approximate thawing times when using this method are:

Pack Size	Thawing Times at Room Temperature (In Pouches)
10 mL	160 minutes

Unopened pouches, thawed at room temperature, may be stored for up to 5 days at 15-25°C.

Prior to use, the product should be warmed to 33-37°C:

Pack Size	33°C to 37°C Incubator (In Pouches)
10 mL	35 minutes

2. Quick Thawing

Thawing on the sterile field using a water bath

33°C to 37°C sterile water bath - transfer plunger and the inner pouch to the sterile field, remove prefilled syringe from inner pouch and place directly into sterile water bath. Ensure the contents of the prefilled syringe are completely immersed under the water.

Approximate thawing times when using this method are:

Pack Size	33°C to 37°C Sterile Water Bath (Pouches Removed)
10 mL	12 minutes

Thawing off the sterile field using a water bath

33°C to 37°C non-sterile water bath in two pouches - maintain the prefilled syringe in both pouches and place into a water bath off the sterile field for appropriate time. Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch with prefilled syringe and plunger onto the sterile field.

Approximate thawing times when using this method are:

Pack Size	33°C to 37°C Non-Sterile Water Bath (In Pouches)
10 mL	80 minutes

Thawing off the sterile field using an incubator

33°C to 37°C incubator in pouches – maintain the prefilled syringe in both pouches and place into an incubator for appropriate time. Remove from incubator after thawing and transfer inner pouch with prefilled syringe and plunger onto the sterile field.

Approximate thawing times when using this method are:

Pack Size	33°C to 37°C Incubator (In Pouches)
10 mL	105 minutes

After thawing, the product must be stored between 15°C and 37°C (room temperature and 37°C).

The product must be used within 12 hours after warming to 33-37°C or removal from original pouches.

Do not use ARTISS unless it is completely thawed and warmed (liquid consistency).

Do not remove the protective syringe cap until use.

DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C.

DO NOT MICROWAVE.

DO NOT REFRIGERATE OR RE-FREEZE.

See *DOSAGE AND ADMINISTRATION, Method of Application (2.3)*.

2.3 Method of Application

Apply ARTISS using the Easyspray and Spray Set, or an equivalent device cleared by FDA for application of ARTISS.

The wound surface should be as dry as possible before application. Wet gloves with saline before handling ARTISS to prevent adherence.

Apply ARTISS as a thin layer. The aerosolized sealant should be applied to the wound in a painting motion from side to side to achieve a single thin application. The wound bed will glisten in the area to which fibrin sealant has been applied. Any areas not covered by fibrin sealant will be clearly visible. The skin graft should be attached to the wound bed immediately after ARTISS has been sprayed. The surgeon has approximately 60 seconds to manipulate and position the graft prior to polymerization.

After the graft has been applied, hold in the desired position by gentle compression for at least 3 minutes to ensure ARTISS sets properly and adheres firmly to the surrounding tissue. The solidified fibrin sealant reaches its ultimate strength in approximately 2 hours after application (70% after 10 minutes).

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 (*see WARNINGS/PRECAUTIONS Application Precautions (5.3)*).

Freeze-Dried: Refer to instructions for use provided with the DUPLOJECT Preparation and Application System.

Frozen: DUO Set Instructions: Firmly connect the two syringe nozzles to the joining piece and secure it by fastening the tether strap to the syringe. Fit an application cannula to the joining piece. To avoid clogging, do not expel the air remaining inside the joining piece or application cannula until application.

Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

3.1 Presentations and Pack Sizes

ARTISS Kit (Freeze-Dried) is supplied as 2 mL, 4 mL and 10 mL (total volume) pack sizes with and without the DUPLOJECT Preparation and Application System. ARTISS (Frozen) is supplied as a 10 mL (total volume) pack size.

3.2 Package Contents

ARTISS Kit (Freeze-Dried)

1. Sealer Protein Concentrate (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile
2. Fibrinolysis Inhibitor Solution (Synthetic), Sterile
3. Thrombin (Human), Vapor Heated, Solvent/Detergent Treated, Freeze-Dried, Sterile
4. Calcium Chloride Solution, Sterile
5. DUPLOJECT Preparation and Application System (if indicated on the carton)

ARTISS (Frozen): Prefilled Syringe

1. [S] Sealer Protein Solution, Vapor Heated, Solvent/Detergent Treated, Sterile
2. [T] Thrombin Solution, Vapor Heated, Solvent/Detergent Treated, Sterile
3. Sterile accessory devices (DUO Set: 1 plunger, 2 joining pieces and 4 application cannulas) are included with each prefilled syringe

The reconstituted solution or prefilled syringe contains:

Sealer Protein Solution

Total protein: 96 – 125 mg/mL
Fibrinogen: 67 – 106 mg/mL
Fibrinolysis Inhibitor (Synthetic): 2250 – 3750 KIU/mL
Other ingredients include: human albumin, tri-sodium citrate, histidine, niacinamide, polysorbate 80 and water for injection (WFI).

Thrombin Solution

Thrombin (Human): 2.5 – 6.5 IU/mL
Calcium Chloride: 36 – 44 µmol/mL
Other ingredients include: human albumin, sodium chloride and water for injection (WFI).

4 CONTRAINDICATIONS

4.1 Intravascular Application

Do not inject ARTISS directly into blood vessels. Intravascular application of ARTISS may result in life-threatening thromboembolic events (*see ADVERSE REACTIONS, Post Marketing (6.3)*).

4.2 Aprotinin Hypersensitivity

ARTISS should not be used in individuals with a known hypersensitivity to aprotinin (*see WARNINGS/PRECAUTIONS, Hypersensitivity/Allergic/Anaphylactic Reactions (5.2) and ADVERSE REACTIONS, Overall Adverse Reactions (6.1)*).

5 WARNINGS/PRECAUTIONS

5.1 Infection Risk from Human Plasma

ARTISS is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses (*see CLINICAL PHARMACOLOGY, Other Clinical Pharmacology Information (9.4)*). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, telephone # 1-800-423-2862. The physician should discuss the risks and benefits of this product with the patient.

Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection) and immune-compromised individuals (*see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1) and PATIENT COUNSELING INFORMATION (17)*).

5.2 Hypersensitivity/Allergic/Anaphylactic Reactions

As with other protein products, hypersensitivity or allergic/anaphylactoid reactions have been reported in <1/100,000 cases. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the fibrin sealant preparation containing aprotinin 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 hypersensitivity reactions. Remove the already applied, polymerized product from the surgical field. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

5.3 Application Precautions

ARTISS is not intended for promoting hemostasis of the donor site.

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

Caution must be used when applying fibrin sealant using pressurized gas. Any application of pressurized gas may be associated with a potential risk of air embolism, tissue rupture or gas entrapment with compression which may be life threatening.

The sealer protein and thrombin solutions can be denatured by alcohol, iodine or heavy metal ions. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of ARTISS.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions

Hypersensitivity/Allergic/Anaphylactic Reactions: As with other protein products, hypersensitivity or allergic/anaphylactoid reactions may occur. In isolated cases, these reactions have progressed to severe anaphylaxis (*see WARNINGS/PRECAUTIONS, Hypersensitivity/Allergic/Anaphylactic Reactions (5.2)*). No adverse events of this type were reported during clinical trials.

6.2 Clinical Trials Experience

The following ADRs have been reported from a clinical trial where ARTISS was used to affix split thickness sheet skin grafts to excised burn wounds (*see CLINICAL STUDIES (11)*). None of the events were classified as serious.

A total of 8 non-serious adverse events (AEs) were deemed related to the use of ARTISS by the investigator. Of the 8 related non-serious AEs, 5 were incidences of skin graft failure: 4 were graft detachment/non-adherence and 1 was graft necrosis. The graft detachment in 2 patients may have been related to the maximum thawing temperature

(40°C) being exceeded during study product preparation. The 3 other non-serious AEs considered related to ARTISS were 2 incidences of pruritus and 1 incidence of dermal cyst. The graft necrosis and the 2 cases of pruritus considered related to ARTISS each had an equivalent AE with the exact start date and severity reported at a control wound where skin grafts were affixed with staples. Therefore, these events are most likely not related to ARTISS, but instead are expected outcomes for any grafted wound regardless of the method of attachment.

Overall, the data collected and analyzed during this study demonstrated that ARTISS is safe for the attachment of sheet skin grafts in subjects with deep partial thickness or full thickness burn wounds.

The ADRs and their frequencies are summarized in the table below:

System Organ Class	Adverse events (Preferred Term)	Number of events/ Number of patients treated
Skin and subcutaneous tissue disorders	Dermal cyst	1/138
	Pruritus	2/138
Injury poisoning and procedural complications	Skin graft failure	5/138

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.3 Post Marketing

The following ADRs reflect what has been reported in post marketing experience with Baxter’s Fibrin Sealants that could reasonably be expected to occur with ARTISS:

Immune system disorders: anaphylactic responses, hypersensitivity

Cardiac disorders: bradycardia, tachycardia

Respiratory, thoracic and mediastinal disorders: dyspnea

Gastrointestinal disorders: nausea

Skin and subcutaneous tissue disorders: urticaria

General disorders and administration site conditions: flushing, impaired healing, edema, pyrexia

Injury, poisoning and procedural complication: seroma

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No formal interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with ARTISS. It is also not known whether ARTISS can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ARTISS should be given to a pregnant woman only if clearly needed.

8.3 Lactating Women

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARTISS is administered to a lactating woman.

8.4 Pediatric Use

In a clinical trial ARTISS was used in 35 pediatric patients aged 1.1 to 16 years to affix skin grafts to burn wounds. Nineteen of these patients were less than or equal to 6 years old. Efficacy and safety in these pediatric patients was not different from an adult population.

8.5 Geriatric Use

Clinical studies of ARTISS did not include any subjects aged 65 and over.

11 DESCRIPTION

ARTISS [Fibrin Sealant], Vapor Heated, Solvent Detergent Treated, (ARTISS) is a two-component fibrin sealant made from pooled human plasma. When combined, the two components, Sealer Protein (Human) and Thrombin (Human), mimic the final stage of the blood coagulation cascade.

ARTISS is intended only for topical administration.

Sealer Protein (Human)

Sealer Protein (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Sealer Protein (Human) is provided either as a freeze-dried powder [Sealer Protein Concentrate (Human)] for reconstitution with Fibrinolysis Inhibitor Solution (Synthetic) or as a frozen liquid solution prefilled into one side of a dual-chambered syringe [S]. The active ingredient in Sealer Protein (Human) is fibrinogen. A Fibrinolysis Inhibitor, Aprotinin (Synthetic) is included in the Sealer Protein (Human) component to delay fibrinolysis. Aprotinin (Synthetic) is manufactured by solid phase synthesis from materials completely of non-human/non-animal origin.

To obtain Sealer Protein (Human), cryoprecipitate derived from the plasma is washed, dissolved in buffer solution, solvent/detergent treated, vapor heat treated, sterile filtered and either freeze-dried in vials or frozen in prefilled syringes.

Thrombin (Human)

Thrombin (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Thrombin (Human) is also provided either as a freeze-dried powder for reconstitution with Calcium Chloride Solution or as a frozen liquid solution prefilled into one side of a dual-chambered syringe [T].

Thrombin is prepared from plasma through a series of separation and filtration steps followed by incubation of the solution with calcium chloride to activate prothrombin to thrombin. The solution subsequently undergoes ultra/diafiltration, vapor heat treatment, solvent/detergent treatment, sterile filtration and either freeze-drying in vials or frozen in prefilled syringes.

Sealer Protein (Human) and Thrombin (Human) are made from pooled human plasma collected at US licensed collection centers. The vapor heat and solvent/detergent treatment steps used in the manufacturing process have been shown to be capable of significant viral reduction. No procedure, however, has been shown to be completely effective in removing viral infectivity from derivatives of human plasma (*see CLINICAL PHARMACOLOGY, Other Clinical Pharmacology Information (9.4) and WARNINGS/PRECAUTIONS, Infection Risk from Human Plasma (5.1)*).

See *DOSAGE FORMS AND STRENGTHS (3)* for available package sizes and presentations.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Upon mixing Sealer Protein (Human) and Thrombin (Human), soluble fibrinogen is transformed into fibrin that adheres to the wound surface and to the skin graft to be affixed. Due to the low thrombin concentration, polymerization of ARTISS will take approximately 60 seconds.

9.2 Pharmacodynamics

Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin. Most of the thrombin is adsorbed by the fibrin, and any excess thrombin is inactivated by protease inhibitors in the blood.

Fibrinolysis Inhibitor, Aprotinin (Synthetic), 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.

9.3 Pharmacokinetics

ARTISS is intended for local application only; therefore, systemic exposure or distribution to other organs or tissues is not expected and Pharmacokinetic Studies were not conducted.

9.4 Other Clinical Pharmacology Information

Viral Clearance

The manufacturing procedure for ARTISS includes processing steps designed to further reduce the risk of viral transmission. In particular, vapor heating and solvent/detergent treatment processes are included in the manufacturing of Sealer Protein Concentrate and Thrombin. Validation studies were conducted using samples drawn from manufacturing intermediates for each of the two human plasma derived components. These samples were spiked with stock virus suspensions of known titers followed by further processing under conditions equivalent to those in the respective manufacturing steps.

The virus reduction factors (expressed as \log_{10}) of independent manufacturing steps were as follows for each of the viruses tested:

Reduction Factors for Virus Removal and/or Inactivation Sealer Protein Component					
Manufacturing Step	Mean Reduction Factors [log ₁₀] of Virus Tested				
	HI V-1	HAV	BVD V	PR V	MMV
Solvent/Detergent Treatment	>5.3	n.d.	>5.7	>5.9	n.d.
Vapor Heat Treatment	>5.5	>5.6	>5.7	>6.7	1.2
Overall Reduction Factor (ORF)	>10.8	>5.6	>11.4	>12.6	1.2
Reduction Factors for Virus Removal and/or Inactivation Thrombin Component					
Manufacturing Step	Mean Reduction Factors [log ₁₀] of Virus Tested				
	HI V-1	HAV	BVD V	PR V	MMV
Thrombin precursor mass capture	n.d.	n.d.	1.8	n.d.	n.d.
Vapor Heat Treatment	>5.5	>4.9	>5.3	>6.7	1.0
Solvent/Detergent Treatment	>5.3	n.d.	>5.5	>6.4	n.d.
Ion Exchange Chromatography	n.d.	n.d.	n.d.	n.d.	3.6
Overall Reduction Factor (ORF)	>10.8	>4.9	>12.6	>13.1	4.6

n.d. = not determined

HIV-1: Human immunodeficiency virus 1; **HAV**: Hepatitis A virus; **BVDV**: Bovine viral diarrhea virus, a model for Hepatitis C virus; **PRV**: Pseudorabies virus, a model for enveloped DNA viruses, among those Hepatitis B virus; **MMV**: Mice minute virus, a model for Human Parvovirus B19.

In addition, Human Parvovirus B19 (B19V) was used to investigate the upstream Thrombin precursor mass capture step and the Thrombin and Sealer Protein vapor

heating steps. Log reduction factors obtained were 1.7 for the Thrombin precursor mass capture step and 1.0 / >4 for the Sealer Protein / Thrombin vapor heating steps, respectively.

10 NONCLINICAL TOXICOLOGY

10.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of ARTISS or studies to determine the effect of ARTISS on fertility have not been performed.

11 CLINICAL STUDIES

ARTISS was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomized, controlled, multicenter clinical study. In each of the 138 patients, two comparable test sites were identified. In one test site the skin graft was fixed with ARTISS; in the other test site the graft was fixed with staples (control). ARTISS proved to be non-inferior to staples with respect to the primary efficacy endpoint, complete wound closure at Day 28 using a one-sided 97.5% confidence interval on the difference in the proportion of test sites successfully treated. Wound closure, defined as full coverage of the wound with a contiguous layer of viable epithelium, was evaluated by a blinded evaluator panel from Day 28 photographs. Results are given in the table below:

Test sites with complete wound closure on Day 28		
	ARTISS	Staples (control)
Intent to Treat Analysis	55 of 127 (43.3%)	47 of 127 (37.0%)
Per Protocol Analysis	48 of 106 (45.3%)	42 of 106 (39.6%)

With respect to secondary endpoints, ARTISS showed a significantly lower incidence and size of hematoma/seroma on Day 1 ($p < 0.0001$ for incidence as well as size). Incidence and area of engraftment on Day 5 and wound closure on Day 14, as well as area of wound closure on Day 28 were not different.

ARTISS was also superior to staples with respect to patient satisfaction ($p < 0.0001$) and patients experienced significantly less anxiety about pain with ARTISS than with staples ($p < 0.0001$). Moreover, ARTISS was significantly superior to staples with respect to the investigator's assessment of quality of graft adherence, preference of fixation method and satisfaction with graft fixation, overall quality of healing and overall rate of healing ($p < 0.0001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

ARTISS is supplied in the following pack sizes and presentations:

Pack Size	NDC Number		
	ARTISS Kit (Freeze-Dried)	ARTISS Kit (Freeze-Dried) with DUPLOJECT System	ARTISS (Frozen)

2 mL	0944-4351-03	0944-4351-04	
4 mL	0944-4351-07	0944-4351-08	
10 mL	0944-4351-11	0944-4351-12	0944-8503-10

See *DOSAGE FORMS AND STRENGTHS, Package Contents (3.2)* for contents.

Storage

ARTISS Kit (Freeze-Dried)

Store at 2°C to 25°C. Avoid freezing. After reconstitution, the product must be used within 4 hours.

ARTISS (Frozen)

Long term: Store at ≤ -20°C.

Short term: Unopened pouches, thawed at room temperature, may be stored for up to 5 days at room temperature (15-25°C) after removal from the freezer. The product must be used within 12 hours after warming to 33-37°C or removal from original pouches. **Do not refrigerate or re-freeze.**

Do not use after the expiration date. Discard if packaging of any components is damaged.

Accessories

The following accessories are available from Baxter Healthcare Corporation. Customer Service: 1-800-423-2090.

FIBRINOTHERM, a combined warming and stirring device for reconstitution of freeze-dried ARTISS

DUPLOJECT Easy Prep Preparation and Application System

Easyspray and Spray Set

17 PATIENT COUNSELING INFORMATION

Because this product is made from human plasma, the physicians should discuss the risks and benefits with the patient. Patients should be encouraged to consult their physician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain (*see WARNINGS/PRECAUTIONS, Infection Risk from Human Plasma (5.1)*)).

Baxter Healthcare Corporation

Westlake Village, CA 91362 USA

US License No. 140

This product, or its use, may be covered by one or more US Patents including US Patent Nos. 4,640,834, 5,962,405 and 5,714,370, 6,579,537 in addition to others including patents pending.

Baxter, FIBRINOTHERM and DUPLOJECT are trademarks of Baxter International Inc., registered in the US Patent and Trademark Office.

ARTISS and Easyspray are trademarks of Baxter International. Inc.

Appendix 2: APLB Review Memo

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: January 29, 2008

From: Jean Makie, M.S., R.D., Regulatory Review Officer
Advertising and Promotional Labeling Branch (APLB) (HFM-602)
Division of Case Management (DCM)

Through: Ele Ibarra-Pratt, RN, MPH, Branch Chief, APLB, HFM-602

To: Pratibha Rana, M.S., RPM, OBRR, DBA, RPMB (HFM-380)
Laura Wood, CMC Committee Chair, OBRR, DH, LBVB (HFM-343)
Kimberly Lindsey, M.D., Medical Officer, OBRR, DH, CRB (HFM-392)

Subject: Labeling Review for Artiss: Comments on draft product labeling
(Full Prescribing Information (FPI), vial, carton, container, and package
labels)
BLA STN: 125266/0

A. REVIEW OF FULL PRESCRIBING INFORMATION (FPI)

We have reviewed the draft Full Prescribing Information (FPI) for ARTISS (ār-'tis), fibrin sealant (human), frozen and lyophilized powder for solution for injection, submitted to BLA STN 125266/0 by Baxter BioScience (Baxter) on June 1, 2007, and offer the following comments.

Recommendations and comments for the HIGHLIGHTS section

Drug names

- Include proprietary name and proper name of biological product. APLB concurs with OBRR's decision to add "(Human)" to the proper name for Artiss, Fibrin Sealant.
- For biologic products, the dosage form and route of administration must be on the next line (i.e., underneath the proper name) since the proper name does not include the drug's dosage form or route of administration. See 21 CFR 600.3 (k) and Section 351 of the PHS Act. Add the "for topical use only" to the established name.

Indications and Usage

- Major limitations of use must be briefly noted in this subsection. APLB recommends that the following statement be added: “Artiss is not indicated for hemostasis (1).” The sponsor proposed a similar statement under Sections 2 and 5.3 of the Full Prescribing Information (FPI). APLB recommends this statement be deleted from these sections and added to section 1 of the FPI.

Dosage and Administration

- We suggest that you use bullets or tabular format to enhance accessibility of information.
- No information is provided regarding the recommended dosage regimen, starting dose, or dose range. This information should be added (reference FPI section 2).
- No information is provided regarding the use of ARTISS (Freeze Dried) within four hours of reconstitution. This information should be added.
- We note that Easyspray is a trademark of Baxter. This device does not appear to be the only one available for use with ARTISS (see FPI section 2.3). The statement can be used to market and promote Baxter’s Easyspray device. The information in Highlights should be revised to state only generalized spray device information.
- Please add the following as the first bullet to this section:
 - For Topical Use Only. Do Not Inject. Apply on surface of prepared wound beds only. (bolded)
- Please make the following the last bullet in this section:
 - Vials are for single use only. Discard unused contents.

Dosage Forms and Strengths

- We recommend the use of bullets or tabular format to enhance accessibility of information.

Contraindications

- Delete “Injection directly into blood vessels” since this information relates to Dosage and Administration and should be located in that subsection of the Highlights (as well as the Dosage and Administration section of the FPI).

Warnings and Precautions

- The bullet “Made from human plasma” should include the potential consequence that makes this a precaution. For example, the bullet could be revised to “This product is made from pooled human plasma which may, theoretically, contain infectious agents.”

Adverse Reactions

- The adverse reactions section should list the most common adverse reactions along with the inclusion criteria. The statement that there were less than 1/100,000 reports of allergic/anaphylactic reactions occurring from use of ARTISS is misleading because it does not reflect the adverse reactions reported in the clinical trials and because the denominator implies a much wider experience with Artiss than has occurred in its clinical development. This section should be revised to be consistent with the adverse reactions seen in the clinical trials for Artiss. For example, “Adverse reactions occurring in greater than 1% of patients treated with Artiss were skin graft failure and pruritus.”
- Anaphylactic reactions are a serious adverse event that is addressed in the warnings section of the FPI. Therefore, it does not need to be included in this subsection.

Drug Interactions

- The statement “None known” minimizes the fact that no drug interaction studies have been performed. This heading is optional and should be omitted from the Highlights section for Artiss.

Use in Specific Populations

- This subsection is reserved for the discussion of clinically important differences in response on specific populations. The pregnancy category should not be included in this subsection of the Highlights and should be deleted.
- Use in Specific Populations is an optional heading and should be omitted from the Highlights section for Artiss.

Recommendations and comments for the FULL PRESCRIBING INFORMATION section

- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning of the FPI in upper-case letters and bold type.
- Ensure that no page header or footer appears in the final FPI document. They now appear in the sponsor’s proposed draft (PDF version).

1 INDICATIONS AND USAGE

- To highlight its importance, APLB recommends moving the limitation of use statement, “Artiss is not indicated for hemostasis,” to this section from the Dosage and Administration section.

2 DOSAGE AND ADMINISTRATION

- Move “Artiss is not indicated for hemostasis” to the Indications and Usage section. (See comment above)
- We suggest deleting “listed in the following table” (line 9) to be consistent with language used in subsequent subsections.

2.1 Preparation of ARTISS Kit (Freeze-Dried)

- Precautionary statements are scattered throughout Section 2.1. To ensure the safe use of ARTISS (Freeze Dried), APLB recommends these statements be prominently displayed together prior to the preparation information.
- Consider the use of a diagrammatic flowchart to assure appropriate preparation and application.
- To ensure the safe use of ARTISS (Freeze Dried) in the surgical setting, APLB recommends deleting this sentence “If a FIBRINOTHERM is not available, contact Baxter...” and replacing with instructions for reconstitution using a water bath or incubator [see those provided for ARTISS (Frozen)].
- Information provided under “Preparation of Sealer Protein Solution” and “Preparation of Thrombin Solution” is specific to the use of the Fibrinotherm device so the subheadings should be revised to include “with FIBRINOTHERM.”
- The placement of the information pertaining to the Fibrinotherm device in section 2.1 detracts from the general preparation information for ARTISS (Freeze Dried). We recommend moving this information to “Preparation of Sealer Protein Solution with FIBRINOTHERM.”
- We recommend deleting the last paragraph in section 2.1 regarding the Fibrinotherm device and inserting it as step 1 under “Preparation of Sealer Protein Solution with FIBRINOTHERM” to ensure that it is used appropriately and does not deter from the safe preparation and administration of ARTISS.
- Under the preparation of solution subsections, the statement “Do not use iodine-containing preparations such as betadine for disinfection” does not provide adequate safety information regarding denaturing by alcohol or heavy metal ions (see section 5.3). APLB suggests that these precautionary statements be appropriately revised to ensure the safe use of ARTISS.

2.2 Preparation of ARTISS Prefilled Syringe (Frozen)

- Precautionary statements are scattered throughout Section 2.2. To ensure the safe use of ARTISS (Frozen), APLB recommends that they be prominently displayed together before the detailed preparation information.
- Delete the numbers preceding the thawing instructions because they imply sequential steps when the information is unique to each method.
- Consider the use of a diagrammatic flowchart to assure appropriate preparation and application.

2.3 Method of Application

- Delete “Easyspray and Spray Set” because it promotes the use of a device that is manufactured by the sponsor but not provided with Artiss packaging.
- No instructions are provided on how to attach the DUPLOJECT or DUO system to the spray device. To ensure the safe administration of ARTISS, APLB recommends that general instructions be added under an “Instructions for Use” section or a statement referring to the spray device’s package instructions be added.
- In sentence two, paragraph two, is the omission of “normal” (e.g., normal saline) before saline an oversight?
- In sentence two, paragraph four, we recommend the addition of “final” to clarify strength of solidified sealant at the end of two hours. Also, is it important for the surgeon to know that ARTISS reaches 70% of its strength in 10 minutes vs. any other time elapse and strength achieved? If this information is critical to the safe application of ARTISS, APLB suggests the use of a table to display relevant solid sealant strengths and set time elapse. Otherwise, the parenthetical statement may be used promotionally.
- The sponsor references the instructions for use provided with the DUPLOJECT system (a copy was provided by sponsor with submission). The DUO set will be included with ARTISS (Frozen) packaging, but only brief instructions are provided in comparison to the detailed package insert for DUPLOJECT. APLB believes comparable instructions for DUO set should be included with ARTISS (Frozen) under an “Instructions for Use” section to ensure the safe administration of the product.
- Consider the use of a diagrammatic flowchart to assure appropriate preparation and application.

4 CONTRAINDICATIONS

4.2 Aprotinin Hypersensitivity

- This contraindication should be revised to command language: “Do not use Artiss in individuals with a known hypersensitivity to aprotinin.”
- Details specific to the hypersensitivity with aprotinin should be included with the contraindication rather than cross-referenced to the Warnings and Precautions section.

5 WARNINGS AND PRECAUTIONS

- Items in this section should be listed in order of importance. Theoretical risks (e.g., viral transmission) should be listed last. Note that the Warnings and Precautions subsection of the Highlights section should reflect the order in this section.

5.1 Infection Risk from Human Plasma

- The sponsor proposes details of viral removal that minimize that fact that there is a risk of viral infection with Artiss. The cross-referencing is unnecessary and serves to further minimize the important message. Suggested wording for this section can be found in *Guidance for Industry: Revised Preventative Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products*. Recommended wording for this section is “This product is a derivative of human plasma. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have been identified for Artiss.”
- The Baxter telephone number does not belong in this section. Suspected viral transmission should be reported to a dedicated company phone line or Medwatch. These numbers are the ones provided in the Highlights section of the FPI.
- Further instruction to physicians regarding the use in pregnant patients belongs in the Pregnancy subsection of the Use in Specific Populations section.
- Further instruction to physicians regarding patient counseling belongs in the Patient Counseling section (Section 17).
- The use in immunocompromised patients appears to be cross-referenced to the Pregnancy subsection of the Special Populations section.

5.2 Hypersensitivity/Allergic/Anaphylactic Reactions

- In sentence one, paragraph one, APLB suggests deleting “As with other protein products” because it minimizes the importance of known reactions related to ARTISS.
- In sentence two, paragraph one, it is unclear that this incidence rate (< 1/100,000 cases) is only from the use of ARTISS, Baxter’s other fibrin sealant (Tisseel), or all other marketed fibrin sealants worldwide or U.S. alone. Additionally, it is unclear if these “cases” are only from clinical trials of ARTISS (See APLB comment under Highlights). APLB suggests that the sponsor be asked to verify this information.
- Delete the term “isolated” because it is vague and can be misleading.
- In sentence three, paragraph one, we recommend that the broad reference to “fibrin sealant preparation containing aprotinin” be replaced with “ARTISS.”

12.5 Application Precautions

- Delete the statement “Artiss is not intended for promoting hemostasis of the donor sight.”
- In sentence one, paragraph two, use command language.
- To ensure the safe application of ARTISS, we suggest adding “and made as dry as possible” to sentence two, paragraph three.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions

- This section must describe the overall adverse reaction profile based on the entire safety database for Artiss. Adverse reactions must be listed in decreasing order of frequency. As stated above, the most common adverse reactions appear to be graft failure and pruritus.
- If applicable, adverse reactions suspected in the product class may be included. In this case, the class adverse reaction is potentially fatal and should be listed here and cross-referenced the hypersensitivity to the Warnings and Precautions.

6.2 Clinical Trials Experience

- The limitations of clinical trial reporting of adverse reactions (lines 252-253) must precede the presentation of adverse reactions for the clinical trials.
- Use “adverse reactions” instead of the abbreviations “ADR” or “AEs” and the term “adverse events.”
- Because minimal adverse events were observed in the clinical trial, the first two paragraphs can be combined to provide more concise safety information.
- The statement “None of the events were classified as serious” should be deleted because it is redundant with the reporting of “non-serious adverse events” and because its placement minimizes the reported adverse reactions that succeed it.
- Is “graft necrosis” correctly categorized as a “non-serious adverse event?”
- Tables containing clinical data should be appropriately cited in the text and labeled accordingly.
- “System Organ Class” is not necessary to the table of adverse reactions considering its brevity.

6.3 Post Marketing

- Baxter markets only Tisseel so “Sealants” should be singular. Also, do not capitalize “Fibrin Sealant” because it can be mistaken for a proprietary name.

7 DRUG INTERACTIONS

- Delete “formal” as it is vague. The sponsor either conducted drug interaction studies or did not.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- APLB suggests replacing the phrase “clearly needed” with “deemed medically necessary” in the last sentence.
- Consider adding wording regarding the Parvovirus precaution to this section since the precaution is specifically directed at pregnant women.

8.4 Pediatric Use

- APLB suggests revising the sentence to “In a clinical trial, the efficacy and safety of ARTISS in pediatric patients was not different from an adult population.” The clinical data should be described in section 14, which currently does not describe any of the study populations.

11 DESCRIPTION

- We recommend deleting the sentence “Artiss is intended only for topical administration.” This information is stated in section 2.
- Delete “for available package sizes and presentations” from the last sentence. The reference to section 3 can stand alone.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

- Avoid using vague terms such as “most” in sentence two, paragraph two. The actual amount of thrombin that is adsorbed should be stated.

12.3 Pharmacokinetics

- To improve clarity, APLB recommends revising this section to “Pharmacokinetic studies were not conducted. Because ARTISS is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.”

12.4 Other Clinical Pharmacology Information

- Appropriately reference the table in the text and label it accordingly.

14. CLINICAL STUDIES

- A description of the overall clinical trial database including overall exposure (number of patients, dose, duration), demographics of exposed population, designs of trial, and any critical exclusions from safety database should be included. Currently, no study populations are described.
- Appropriately cite the table in the text and label it accordingly.
- Given the actual number of patients in the clinical trial, the percentages provided in the table may be used promotionally and could be misleading. Consider replacing with statistics.
- APLB agrees with the Medical Officer’s recommendation to delete the sentences pertaining to secondary endpoints, which may be used promotionally if permitted to remain.
- In the last paragraph, were the satisfaction ratings primary endpoints? If not, we recommend deleting the paragraph as the superiority claims to staple usage may be used promotionally.

16 HOW SUPPLIED/STORAGE AND HANDLING

- In the sentence following the table, delete “for contents” because it is not needed.
- In the table, add “with Duo Set” to ARTISS (Frozen) because the device is always supplied with this formulation.
- Delete the information under “Accessories.” It is promotional for the sponsor’s other products that are not provided in ARTISS packaging.

17 PATIENT COUNSELING INFORMATION

- In Sentence one, “physicians” should be singular.
- Use command language: replace “encouraged” with “instructed” in sentence two.

Instruction for Use

- See APLB comments regarding the inclusion of instructions for use for the DUO set and spray device above.

B. REVIEW OF VIAL, CARTON, CONTAINER, AND PACKAGE LABELS

Baxter provided copies of the ARTISS and diluent vial, carton, container, and package (pouch) labels in the original BLA, submitted on June 1, 2007. ARTISS will be supplied as lyophilized powder for reconstitution to final volume of 2, 4, and 10 mL in single-use vials [referred to as ARTISS (Freeze Dried)] and as frozen, 10 mL -----

[referred to as ARTISS (Frozen)]. Additionally, the sponsor submitted package labeling

for the DUPLOJECT (Fibrin Sealant Preparation and Application System) which will be available separately or supplied with ARTISS (Freeze Dried) and package labeling for the DUO Set 10 mL, which will be supplied with ARTISS (Frozen).

General Comments:

- APLB reviewed the ARTISS and diluent vial, carton, container, and package (pouch) labels and they do not appear to contain unsupported promotional claims.
- APLB reviewed the package labels for DUPLOJECT (Fibrin Sealant Preparation and Application System) and the DUO Set 10 mL and they do not appear to contain unsupported promotional claims.

ARTISS (Freeze Dried) Comments:

Container labels

- The container labels for the ARTISS (Freeze Dried) kit are not compliant with the regulations because they omit information that is required by the regulations. We note that the sponsor submitted mock labels for ARTISS (Freeze Dried), 2 mL only. The following comments, therefore, also apply to labels for ARTISS (Freeze Dried), 4 and 10 mL.
 - The Sealer Protein Concentrate (Human), Thrombin (human), Fibrinolysis Inhibitor Solution (diluent), and Calcium Chloride Solution (diluent) container labels omit the statement “Rx only.” See 21 CFR 610.60(a)(6).

Carton labels

- The carton labels for the ARTISS (Freeze Dried) kit are not compliant with the regulations because they omit information that is required by the regulations. The sponsor submitted mock labels for ARTISS (Freeze Dried), 2 mL only. The following comments, therefore, also apply to labels for ARTISS (Freeze Dried), 4 and 10 mL.
 - The proper name should include “(Human)”. See 21 CFR 610.61(a)
 - The carton labeling omits preservative information. The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the label should include “no preservative” should be included. See 21 CFR 610.61(e).
 - The carton labeling omits route of administration information. The statement “FOR TOPICAL USE ONLY” should be added. See 21 CFR 610.61(k)
 - The carton labeling omits information pertaining to the known sensitizing substance or reference to an enclosed circulation containing appropriate information. Section 5.2 of the Full Prescribing Information (FPI) states:

“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.”

Information pertaining to aprotinin hypersensitivity should be appropriately stated. See 21 CFR 610.61(l)

Sleeve label

- The label for the ARTISS (Freeze Dried) kit sleeve is not compliant with the regulations because they omit information that is required by the regulations.
 - The proper name should include “(Human)”. See 21 CFR 610.61(a)
 - The sleeve labeling omits lot information and an expiration date. See 21 CFR 610.61(c) and 21 CFR 610.61(d), respectively.
 - The sleeve labeling omits route of administration information. The statement “FOR TOPICAL USE ONLY” should be added. See 21 CFR 610.61(k)

ARTISS (Frozen) Comments:

Container labels

- The container (syringe) label for ARTISS (Frozen) is not compliant with the regulations because it omits information that is required by the regulations.
 - The proper name should include “(Human)”. See 21 CFR 610.60(a)(1)
 - The label omits the statement “Rx only.” See 21 CFR 610.60(a)(6)

Carton labels

- The ARTIS (Frozen) carton labels are not compliant with the regulations because they omit information that is required by the regulations.
 - The proper name should include “(Human)”. See 21 CFR 610.61(a)
 - The carton labeling omits preservative information. The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the rods “no preservative” should be included. See 21 CFR 610.61(e).
 - The carton labeling omits route of administration information. The statement “FOR TOPICAL USE ONLY” should be added. See 21 CFR 610.61(k)
 - The carton labeling omits information pertaining to the known sensitizing substance or reference to an enclosed circulation containing appropriate information. Information pertaining to aprotinin hypersensitivity should be appropriately stated. See 21 CFR 610.61(l)
 - ARTISS (Frozen) should not be microwaved. The carton labeling omits this information. To ensure the safe use and administration of this product, we recommend revising the statement “Do not refrigerate or re-freeze.” to “Do not refrigerate, microwave, or re-freeze.” See 21 CFR 610.61(i)

DUPLOJECT and DUO Set 10 mL Comments

- The DUPLOJECT carton labels are not compliant with the regulations because they omit information that is required by the regulations.
 - The proper name for ARTISS should include “(Human)”. See 21 CFR 610.61(a)
- The DUPLOJECT package labels are not compliant with the regulations because they omit information that is required by the regulations.
 - The proper name for ARTISS should include “(Human)”. See 21 CFR 610.61(a)
- The DUO Set package labels are not compliant with the regulations because they omit information that is required by the regulations.
 - The DUO Set package label omits information pertaining to adequate directions for use (e.g., directions under which the device can be used safely and for the purposes for which it is intended; lot and expiration date information). To ensure the safe use of this device and the subsequent safe administration of ARTISS (Frozen), we suggest diagrammatic instructions comparable to that of the DUPLOJECT be considered. See 21 CFR 801.5

The above comments have been provided from a comprehension and promotional perspective. If you have any questions with regards to this review please contact Jean Makie, M.S., R.D., Regulatory Review Officer at 301-827-3028