

## 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 (Human)]

#### For Topical Use Only

Frozen solution and lyophilized powder for solution for topical application

Initial U.S. Approval: 2008

#### RECENT MAJOR CHANGES

Indications and Usage (1.2)	08/2011
Dosage and Administration (2.3)	08/2011
Adverse Reactions (6.1)	08/2011

#### INDICATIONS AND USAGE

- ARTISS is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and pediatric populations greater than or equal to 1 year of age(1.1)
- ARTISS is indicated to adhere tissue flaps during facial rhytidectomy surgery (face-lift) (1.2)
- ARTISS is not indicated as an adjunct to hemostasis (1)

#### DOSAGE AND ADMINISTRATION

For Topical Use Only. Do Not Inject (2). Apply on surface of prepared wound beds only (2.3)

ARTISS Kit (Freeze-Dried) requires reconstitution prior to use (2.1)  
ARTISS Pre-filled Syringe (Frozen) requires thawing prior to use (2.2)

Apply as a thin layer using the Easyspray and Spray Set (2.3, 5.3)  
Dosage: 2 mL will cover approximately 100 cm<sup>2</sup> surface area (2)

Vials and pre-filled syringes are for single use only. Discard unused contents (2.3)

#### DOSAGE FORMS AND STRENGTHS

ARTISS is available as a two-component fibrin sealant, including Sealer Protein (Human) and Thrombin (Human), in two dosage forms, 2 mL, 4 mL and 10 mL Freeze-Dried Kit and 2 mL, 4 mL and 10 mL Frozen Solution in Pre-filled Syringe (3)

#### CONTRAINDICATIONS

- Do not inject directly into the circulatory system (4.1)
- Do not use in individuals with a known hypersensitivity to aprotinin (4.2, 5.1)

#### WARNINGS AND PRECAUTIONS

- Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of ARTISS (5.1)
- Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the surface of the tissue (5.2) Exposure to solutions containing alcohol, iodine or heavy metals may cause ARTISS to be denatured (5.3)
- Apply only as thin layer (2.3, 5.3)
- ARTISS is made from human plasma and may contain infectious agents, e.g., viruses and theoretically, Creutzfeldt-Jacob disease (CJD) agent. (5.4)

#### ADVERSE REACTIONS

Adverse reactions reported during clinical trials in greater than 1% for subjects were:

**Burns:** skin graft failure, hematoma and pruritus (6.1)

**Facial Rhytidectomy:** hematoma/seroma (6.1)

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](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

Pregnancy: No human or animal data. Use ARTISS only if clearly needed (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2011

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1 **Baxter Healthcare Corporation**

2 **FULL PRESCRIBING INFORMATION**

3 ARTISS [Fibrin Sealant (Human)]

4 **1 INDICATIONS AND USAGE**

5 **1.1 Burns**

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

8  
9 **1.2 Facial Rhytidectomy**

10 ARTISS is indicated to adhere tissue flaps during facial rhytidectomy surgery (face-lift).

11  
12 ARTISS is not indicated as an adjunct to hemostasis.

13  
14 **2 DOSAGE AND ADMINISTRATION**

15 **FOR TOPICAL USE ONLY – DO NOT INJECT.**

16  
17 The amount of ARTISS to be applied must be individualized by the treating physician based on the size of the  
18 surface to be covered. The approximate surface areas covered by each package size of ARTISS are:

**Table 1.**

<b>Approximate area requiring skin graft fixation</b>	<b>Required package size of ARTISS</b>
100 cm <sup>2</sup>	2 mL
200 cm <sup>2</sup>	4 mL
500 cm <sup>2</sup>	10 mL

19 It is recommended that every time a patient receives a dose of ARTISS the name and lot number (batch  
20 number) of the product are documented in order to maintain a link between the patient and product batch.

21  
22 **2.1 Preparation of ARTISS Kit (Freeze-Dried)**

23 **During preparation of ARTISS Kit:**

24  
25 **DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C**

26 **DO NOT REFRIGERATE OR FREEZE AFTER RECONSTITUTION**

27  
28 **Do not use iodine or heavy metal containing preparations such as betadine for disinfection of vial  
29 stoppers. Allow alcohol-based disinfectants to evaporate before puncturing stopper.**

30  
31 After reconstitution, the product must be used within 4 hours.

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

34  
35 ARTISS Kit contains the following substances in four separate vials:

- 36 - Sealer Protein Concentrate (Human)
- 37 - Fibrinolysis Inhibitor Solution (Synthetic)
- 38 - Thrombin (Human)
- 39 - Calcium Chloride Solution

40  
41  
42 Freeze-dried Sealer Protein Concentrate and Thrombin are reconstituted in Fibrinolysis Inhibitor Solution and  
43 Calcium Chloride Solution, respectively. The Sealer Protein Solution and Thrombin Solution are then  
44 combined using the DUPLOJECT Preparation and Application System, or an equivalent delivery device cleared  
45 by FDA for use with ARTISS to form the Fibrin Sealant.

46

### 47 **Prewarming ARTISS Kit with FIBRINOTHERM**

48 If a FIBRINOTHERM device is not available, contact Baxter (1-800-423-2090) for assistance. See  
49 FIBRINOTHERM manual for complete operating instructions.

- 50 1. Plug the FIBRINOTHERM Heating and Stirring Device into an electrical socket and activate the  
51 warmer (amber switch). Ensure that the stirring mechanism of the FIBRINOTHERM device is initially  
52 switched off (green switch).
- 53 2. Place all four vials from the ARTISS Kit into the prewarmed wells of the FIBRINOTHERM, using the  
54 appropriately sized adapter rings, and allow the vials to warm for up to 5 minutes (room temperature  
55 product may take less time).

56

### 57 **Preparation of Sealer Protein Solution with FIBRINOTHERM**

- 58 1. Remove the flip-off caps from the vial containing the Sealer Protein Concentrate and the vial containing  
59 the Fibrinolysis Inhibitor Solution, disinfect the rubber stoppers of both vials with a germicidal solution  
60 and allow to dry.
- 61 2. Transfer the Fibrinolysis Inhibitor Solution into the vial containing the freeze-dried Sealer Protein  
62 Concentrate using the sterile reconstitution components provided with the DUPLOJECT Preparation and  
63 Application System, or an equivalent device cleared by FDA for use with ARTISS (see directions  
64 provided with the device system for specific reconstitution instructions). Gently swirl the vial to ensure  
65 that the freeze-dried material is completely soaked.
- 66 3. Place the vial into the largest opening of the FIBRINOTHERM device with the appropriate adaptor.  
67 Switch on the stirrer (green switch) and allow the vial contents to stir until all Sealer Protein Concentrate  
68 is dissolved.
- 69 4. Reconstitution of the freeze-dried Sealer Protein Concentrate is complete as soon as no undissolved  
70 particles are visible. Otherwise, return the vial to the FIBRINOTHERM device and agitate for a few  
71 more minutes until the solution appears homogeneous.

72

### 73 **Notes:**

- 74 - Do not use the Sealer Protein Concentrate until it has fully dissolved. If the Sealer Protein Concentrate  
75 has not dissolved within 20 minutes using the FIBRINOTHERM device, discard the vial and prepare a  
76 fresh kit. Excessive stirring (20 minutes or more) may compromise product quality.
- 77 - If not used promptly, keep the Sealer Protein Solution at 37°C without stirring. To ensure homogeneity,  
78 switch on the stirrer of the FIBRINOTHERM device shortly before drawing up the solution.

79

### 80 **Preparation of Thrombin Solution with FIBRINOTHERM**

- 81 1. Remove the flip-off caps from the vial containing Thrombin and the vial containing Calcium Chloride  
82 Solution, disinfect the rubber stoppers of both vials with a germicidal solution and allow to dry.
- 83 2. Transfer the contents of the vial with Calcium Chloride Solution into the vial containing the freeze-dried  
84 Thrombin using the sterile reconstitution components provided with the DUPLOJECT Preparation and  
85 Application System, or an equivalent device cleared by FDA for use with ARTISS (see directions  
86 provided with the device system for specific reconstitution instructions).
- 87 3. Swirl briefly.
- 88 4. Place the vial into the adapted opening of the FIBRINOTHERM device.
- 89 5. Reconstitution of Thrombin is complete when all of the Thrombin concentrate is dissolved.
- 90 6. Keep the Thrombin Solution at 37°C until used.

91

### 92 **Transferring to the Sterile Field**

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

96  
97 **2.2 Preparation of ARTISS Pre-filled Syringe (Frozen)**

98 **During preparation of ARTISS (frozen):**

99  
100 **DO NOT EXPOSE TO TEMPERATURES ABOVE 37°C**

101 **DO NOT MICROWAVE**

102 **DO NOT REFRIGERATE OR RE-FREEZE AFTER THAWING**

103  
104 Do not use ARTISS (frozen) unless it is completely thawed and warmed (liquid consistency).

105 Do not remove the protective syringe cap until thawing is complete and the application tip is ready to be  
106 attached.

107  
108 ARTISS (frozen) can be prepared (thawed) using one of two options:

109  
110 **Room Temperature Thawing**

111 Approximate thawing times when using this method are:

112

Pack Size	Room Temperature (In Pouches)
2 mL	60 minutes
4 mL	110 minutes
10 mL	160 minutes

113  
114 Unopened pouches, thawed at room temperature, may be stored for up to 14 days at 15-25°C.

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

116

Pack Size	33°C to 37°C Incubator (In Pouches)
2 mL	15 minutes
4 mL	25 minutes
10 mL	35 minutes

117  
118 **Quick Thawing**

119 Thawing on the sterile field using a water bath

120 33°C to 37°C sterile water bath - transfer the inner pouch to the sterile field, remove pre-filled syringe from  
121 inner pouch and place directly into sterile water bath. Ensure the contents of the pre-filled syringe are  
122 completely immersed under the water.

123  
124 Approximate thawing times when using this method are:

Pack Size	33°C to 37°C Sterile Water Bath (Pouches Removed)
2 mL	5 minutes
4 mL	5 minutes
10 mL	12 minutes

125  
126 Thawing off the sterile field using a water bath

127 33°C to 37°C non-sterile water bath in two pouches - maintain the pre-filled syringe in both pouches and place  
128 into a water bath off the sterile field for appropriate time. Ensure the pouches remain submerged throughout  
129 thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch with pre-filled  
130 syringe onto the sterile field.

131  
132 Approximate thawing times when using this method are:

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

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

133

134 Thawing off the sterile field using an incubator

135 33°C to 37°C incubator in pouches – maintain the pre-filled syringe in both pouches and place into an incubator  
 136 for appropriate time. Remove from incubator after thawing and transfer inner pouch with pre-filled syringe  
 137 onto the sterile field.

138

139 Approximate thawing times when using this method are:

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

140 Maintain the product at 33-37°C until use. If product is removed from original pouch or warmed to 33-37°C it  
 141 must be used within 12 hours.

142

143 **2.3 Method of Application**

144 Apply ARTISS using the Easyspray and Spray Set, or an equivalent device cleared by FDA for application of  
 145 ARTISS. See additional instructions for use provided with the spray set.

146

147 The wound surface should be as dry as possible before application.

148

149 Ensure that parts of the body outside the desired application area are sufficiently covered to prevent tissue  
 150 adherence at undesired site.

151

152 Apply ARTISS as a thin layer to avoid the formation of excess granulation tissue and to ensure gradual  
 153 absorption of the polymerized fibrin sealant.

154

155 The aerosolized sealant should be applied to the wound in a painting motion from side to side to achieve a  
 156 single thin application. The wound bed will glisten in the area to which fibrin sealant has been applied.

157

158 Any areas not covered by fibrin sealant will be clearly visible.

159

160 The skin flap or graft should be attached to the wound bed immediately after ARTISS has been sprayed. The  
 161 surgeon has up to 60 seconds to manipulate and position the flap or graft prior to polymerization. The initial  
 162 amount of the product to be applied should be sufficient to cover the intended application area.

163

164 The application can be repeated, if necessary, to any small areas that may not have been previously treated. To  
 165 prevent adherence, wet gloves with normal saline before product contact.

166

167 After the flap or graft has been positioned, hold in the desired position by gentle compression for at least 3  
 168 minutes to ensure ARTISS sets properly and adheres firmly to the surrounding tissue. The solidified fibrin  
 169 sealant reaches its final strength in approximately 2 hours after application.

170

171 The cannulas included with the DUPLOJECT Preparation and Application System or DUO Set may be used for  
 172 small wounds or for edges of a skin graft that did not adhere to the wound bed (*see WARNINGS AND*  
 173 *PRECAUTIONS, Application Precautions (5.3)*). Immediately before application, expel and discard the first  
 174 several drops from the application cannula to ensure adequate mixing of the Sealer Protein and Thrombin  
 175 solutions in cases where very small volumes (1-2 drops) are administered.

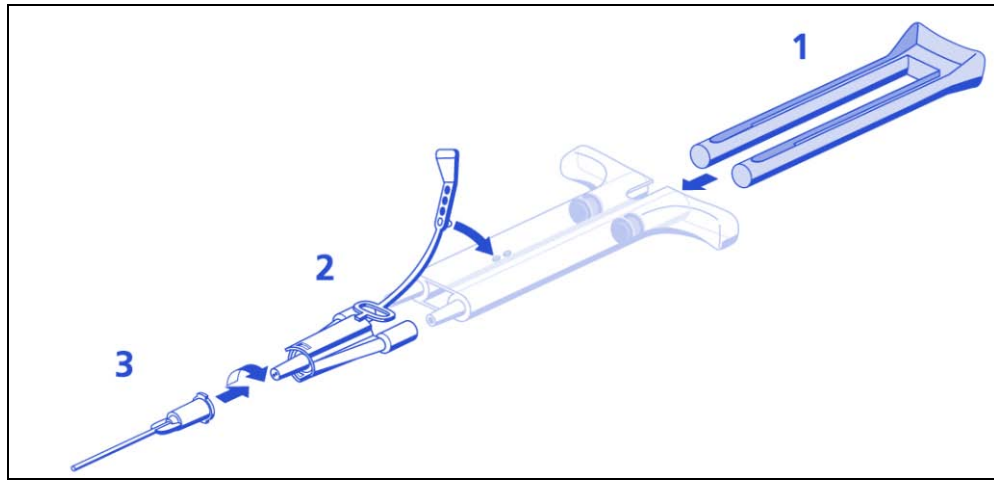
Freeze-Dried: Refer to instructions for use provided with the DUPLOJECT Preparation and Application System.

Frozen: DUO Set Instructions (see Figure 1 below):

1. Insert plunger into syringe barrel.
2. Firmly connect the two syringe nozzles to the joining piece and secure it by fastening the tether strap to the syringe.
3. Fit an application cannula to the joining piece.

If application of ARTISS is interrupted, replace the cannula immediately before application is resumed.

**Figure 1.**  
**DUO SET A**



Vials and pre-filled syringes are for single use only. Discard unused contents.

### 3 DOSAGE FORMS AND STRENGTHS

ARTISS is available as a two-component fibrin sealant, including Sealer Protein (Human) and Thrombin (Human), in two dosage forms 2 mL, 4 mL and 10 mL Freeze-Dried Kit and 2 mL, 4 mL and 10 mL Frozen Solution in Pre-filled Syringe.

The reconstituted solution or pre-filled 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 units/mL\*

Calcium Chloride: 36 – 44  $\mu$ mol/mL

Other ingredients include: human albumin, sodium chloride and water for injection (WFI).

\* The potency expressed in units is determined using a clotting assay against an internal reference standard for potency that has been calibrated against the World Health Organization (WHO) Second International Standard for Thrombin, 01/580. Therefore, a unit (U) is equivalent to an International Unit (IU).

### 4 CONTRAINDICATIONS

214 **4.1 Intravascular Application**

215 **Do not inject ARTISS directly into blood vessels. Intravascular application of ARTISS may result in life-**  
216 **threatening thromboembolic events.**

217

218 **4.2 Aprotinin Hypersensitivity**

219 Do not use ARTISS in individuals with a known hypersensitivity to aprotinin and/or hypersensitivity to any of  
220 the active substances or excipients (*see WARNINGS AND PRECAUTIONS,*  
221 *Hypersensitivity/Allergic/Anaphylactic Reactions (5.1) and ADVERSE REACTIONS (6)*).

222

223 **5 WARNINGS AND PRECAUTIONS**

224 **5.1 Hypersensitivity/Allergic/Anaphylactic Reactions**

225 Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of ARTISS. Cases have been  
226 reported in post-marketing experience with fibrin sealant (*see ADVERSE REACTIONS, Post-Marketing*  
227 *Experience (6.2)*). In specific cases, these reactions have progressed to become life-threatening. Such reactions  
228 may especially be seen if ARTISS is applied repeatedly over time or in the same setting, or if systemic aprotinin  
229 has been administered previously; however, these reactions may also occur in patients receiving ARTISS for the  
230 first time. Even if the first treatment was well tolerated, a subsequent administration of ARTISS or systemic  
231 aprotinin may not exclude the occurrence of an allergic reaction. Symptoms associated with allergic  
232 anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or  
233 bradycardia, dyspnea, severe hypotension and anaphylactic shock.

234

235 Aprotinin is included in ARTISS for its antifibrinolytic properties. Aprotinin, a monomeric polypeptide, is  
236 known to be associated with anaphylactic reactions. Even in the case of strict local application of aprotinin,  
237 there is a risk of anaphylactic reactions to aprotinin, particularly in the case of previous exposure (*see*  
238 *CONTRAINDICATIONS, Aprotinin Hypersensitivity (4.2)*).

239

240 Discontinue administration of ARTISS in the event of anaphylactic/-oid or hypersensitivity reactions. Remove  
241 the already applied, polymerized product from the surgical field. Mild reactions can be managed with  
242 antihistamines. Severe reactions and reactions involving hypotension require immediate resuscitative  
243 intervention.

244

245 **5.2 Air or Gas Embolism**

246 Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer  
247 fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended  
248 pressures and in close proximity to the tissue surface.

249

250 When applying ARTISS using a spray device, be sure to use the pressure within the pressure range  
251 recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using  
252 pressure above 20-25 psi. Do not spray closer than the distance recommended by the spray device  
253 manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the  
254 surface of the tissue. When spraying ARTISS, changes in blood pressure, pulse, oxygen saturation and end  
255 tidal CO<sub>2</sub> should be monitored because of the possibility of occurrence of air or gas embolism. When using the  
256 Easyspray device, or an equivalent spray device cleared by FDA, use the pressure within the pressure range  
257 recommended by the spray device manufacturer. Spray ARTISS only on to visible application sites.

258

259 **5.3 Application Precautions**

260 The sealer protein and thrombin solutions can be denatured by alcohol, iodine or heavy metal ions (e.g.  
261 antiseptic solutions). If any of these substances have been used to clean the wound area, the area must be  
262 thoroughly rinsed before application of ARTISS and made as dry as possible.

263

264 Apply ARTISS as a thin layer. Excessive clot thickness may delay the natural wound healing process.

265

#### 266 **5.4 Infection Risk from Human Plasma**

267 ARTISS is made from human plasma. Products made from human plasma may contain infectious agents, such  
268 as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been  
269 reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain  
270 current virus infections, and by inactivating and removing certain viruses. Despite these measures, such  
271 products can still potentially transmit disease. Because this product is made from human blood, it may carry a  
272 risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.  
273 This also applies to unknown or emerging viruses or other pathogens. All infections thought by a physician  
274 possibly to have been transmitted by this product should be reported by the physician or other healthcare  
275 provider to Baxter Healthcare Corporation, telephone # 1-866-888-2472.

276

277 Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus  
278 B19 most seriously affects pregnant women (fetal infection), immune-compromised individuals or individuals  
279 with an increased erythropoiesis (e.g., hemolytic anemia) (see *USE IN SPECIFIC POPULATIONS, Pregnancy*  
280 *(8.1)* and *PATIENT COUNSELING INFORMATION (17)*).

281

### 282 **6 ADVERSE REACTIONS**

283 The most frequent ( $\geq 1\%$  of clinical study subjects) adverse reactions with the use of ARTISS were: skin graft  
284 failure, hematoma and pruritus in burn studies, and hematoma/seroma in rhytidectomy studies.

285

286

#### 287 **6.1 Clinical Trials Experience**

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

291

292 The burn and rhytidectomy surgery studies were prospective, randomized, controlled, multicenter clinical  
293 studies with a total of 298 subjects. In each study the subject served as its own control. All subjects treated  
294 have been included into the safety analysis. See *CLINICAL STUDIES (14)* for outcome.

295

296 The data described in Table 2 reflects the exposure to ARTISS in the 4 burn and rhytidectomy surgery studies:

297

298

**Table 2.**

<b>Study Population Demographics</b>				
<b>Parameter</b>	<b>Burn</b>		<b>Rhytidectomy</b>	
	<b>Preliminary Study</b>	<b>Confirmatory Study</b>	<b>Preliminary Study</b>	<b>Confirmatory Study</b>
<b>Sample size (N)</b>	40	138	45	75
<b>Gender</b>				
<b>F (%) /</b>	11 (27.5%)	44 (31.9%)	42 (93.3%)	71 (94.7%)
<b>M (%)</b>	29 (72.5%)	94 (68.1%)	3 (6.7%)	4 (5.3%)
<b>Age Range</b> <b>(years)</b>	6 – 55	1 – 63	43 – 70	40 - 71
<b>Volume</b> <b>applied</b> <b>(Mean <math>\pm</math> SD)</b> <b>(Range in mL)</b>	2.9 $\pm$ 1.64 (Range: 1.0 - 10.8)	2.7 $\pm$ 1.9 (Range: 0.2 - 12.0)	2.32 $\pm$ 0.95 (Range: 0.80 - 4.0)	2.58 $\pm$ 1.17 (Range: 0.60 - 4.0)

299

300 Adverse reactions in the burn studies occurring in greater than 1% of subjects treated with ARTISS were skin  
301 graft failure (3%), hematoma (1%) and pruritus (1%) [n=178].

302

303 Adverse reactions in the facial rhytidectomy studies occurring in greater than 1% of subjects treated with  
304 ARTISS were hematoma/seroma (4%) [n = 120].

305  
306 In the facial rhytidectomy studies, three subjects experienced serious adverse events (experiences). Two were  
307 local: wound abscess on the ARTISS treated side of the face that was recognized on postoperative day 14 and  
308 was treated by operative incision and drainage; and a case of basal cell carcinoma on the SoC treated side of the  
309 face. A third subject experienced dehydration on the second postoperative day.

## 310 311 **6.2 Post-Marketing Experience**

312 *The following adverse reactions have been identified during post approval use of ARTISS. Because these*  
313 *reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably*  
314 *estimate their frequency or establish a causal relationship to drug exposure.*

315  
316 Fatal air embolism has been reported with misapplication of fibrin sealants administered with a pressurized  
317 spray device.

318  
319 The following adverse reactions have been reported in post-marketing experience with another Baxter fibrin  
320 sealant that could reasonably be expected to occur with ARTISS:

321  
322 **Immune system disorders:** anaphylactic responses, hypersensitivity

323 **Cardiac disorders:** bradycardia, tachycardia

324 **Respiratory, thoracic and mediastinal disorders:** dyspnea

325 **Gastrointestinal disorders:** nausea

326 **Skin and subcutaneous tissue disorders:** urticaria

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

328 **Injury, poisoning and procedural complication:** seroma

329

## 330 **7 DRUG INTERACTIONS**

331 Oxycellulose containing preparations may reduce the efficacy of ARTISS and should not be used as carrier  
332 materials. No interaction studies have been performed.

333

## 334 **8 USE IN SPECIFIC POPULATIONS**

### 335 **8.1 Pregnancy**

#### 336 **Pregnancy Category C**

337 Animal reproduction studies have not been conducted with ARTISS. It is also not known whether ARTISS can  
338 cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Some viruses,  
339 such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most  
340 seriously affects pregnant women (fetal infection). ARTISS should be given to a pregnant woman only if  
341 deemed medically necessary.

342

### 343 **8.3 Nursing Mothers**

344 It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk,  
345 caution should be exercised when ARTISS is administered to nursing mothers.

346

### 347 **8.4 Pediatric Use**

348 In two clinical trials utilizing ARTISS to adhere autologous skin grafts to surgically prepared wound beds  
349 resulting from burns, the efficacy and safety of ARTISS in 38 pediatric subjects (27 subjects ages 1 through 10  
350 years and 11 subjects ages 11 through 16 years) were not different from an adult population.

351

### 352 **8.5 Geriatric Use**

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

355

## 356 **10 OVERDOSAGE**

357 To avoid the formation of excess granulation tissue and to ensure gradual absorption of the polymerized fibrin  
358 sealant, apply only a thin layer of ARTISS (see *DOSAGE AND ADMINISTRATION, Method of Application*  
359 *(2.3)*).

360

## 361 **11 DESCRIPTION**

362 ARTISS [Fibrin Sealant (Human)] is a two-component fibrin sealant made from pooled human plasma.

363

### 364 **Sealer Protein (Human)**

365 Sealer Protein (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made  
366 from pooled human plasma. Sealer Protein (Human) is provided either as a freeze-dried powder [Sealer Protein  
367 Concentrate (Human)] for reconstitution with Fibrinolysis Inhibitor Solution (Synthetic) or as a frozen liquid  
368 solution pre-filled into one side of a dual-chambered syringe (1). The active ingredient in Sealer Protein  
369 (Human) is fibrinogen. A Fibrinolysis Inhibitor, Aprotinin (Synthetic) is included in the Sealer Protein  
370 (Human) component to delay fibrinolysis. Aprotinin (Synthetic) is manufactured by solid phase synthesis from  
371 materials completely of non-human/non-animal origin.

372

### 373 **Thrombin (Human)**

374 Thrombin (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made  
375 from pooled human plasma. Thrombin (Human) is also provided either as a freeze-dried powder for  
376 reconstitution with Calcium Chloride Solution or as a frozen liquid solution pre-filled into one side of a dual-  
377 chambered syringe (2).

378

379 Sealer Protein (Human) and Thrombin (Human) are made from pooled human plasma collected at US licensed  
380 collection centers. The vapor heat and solvent/detergent treatment steps used in the manufacturing process have  
381 been shown to be capable of significant viral reduction. No procedure, however, has been shown to be  
382 completely effective in removing viral infectivity from derivatives of human plasma (*see Viral Clearance below*  
383 *and WARNINGS AND PRECAUTIONS, Infection Risk from Human Plasma (5.4)*).

384

### 385 **Viral Clearance**

386 The manufacturing procedure for ARTISS includes processing steps designed to further reduce the risk of viral  
387 transmission. In particular, vapor heating and solvent/detergent treatment processes are included in the  
388 manufacturing of Sealer Protein Concentrate and Thrombin. Validation studies were conducted using samples  
389 drawn from manufacturing intermediates for each of the two human plasma derived components. These  
390 samples were spiked with stock virus suspensions of known titers followed by further processing under  
391 conditions equivalent to those in the respective manufacturing steps. The stock virus suspensions represent  
392 HIV, HBV, HCV, HAV and Human Parvovirus B19.

393 The virus reduction factors (expressed as  $\log_{10}$ ) of independent manufacturing steps are shown in Table 3 for  
394 each of the viruses tested:

395

**Table 3.**

<b>Reduction Factors for Virus Removal and/or Inactivation Sealer Protein Component</b>					
Manufacturing Step	Mean Reduction Factors [ $\log_{10}$ ] of Virus Tested				
	HIV-1	HAV	BVDV	PRV	MMV
Early Manufacturing Steps	n.d.	n.d.	n.d.	n.d.	2.7

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	3.9
<b>Reduction Factors for Virus Removal and/or Inactivation Thrombin Component</b>					
	Mean Reduction Factors [ $\log_{10}$ ] of Virus Tested				
Manufacturing Step	HIV-1	HAV	BVDV	PRV	MMV
Thrombin precursor mass capture	3.2	1.5	1.8	2.5	1.2
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)	>14.0	>6.4	>12.6	>15.6	5.8

396 n.d. = not determined

397

398 **HIV-1:** Human immunodeficiency virus 1; **HAV:** Hepatitis A virus; **BVDV:** Bovine viral diarrhea virus, a  
399 model for Hepatitis C virus; **PRV:** Pseudorabies virus, a model for enveloped DNA viruses, among those  
400 Hepatitis B virus; **MMV:** Mice minute virus, a model for B19V.

401

402 In addition, Human Parvovirus B19 was used to investigate the upstream Thrombin precursor mass capture  
403 step, the Sealer Protein early manufacturing steps and the Thrombin and Sealer Protein vapor heating steps.  
404 Using quantitative PCR assays, the estimated log reduction factors obtained were 1.7 and 3.4 for the Thrombin  
405 precursor mass capture step and Sealer Protein early manufacturing steps and >4 / 1.0 for the Thrombin / Sealer  
406 Protein vapor heating steps, respectively.

407

408 See *DOSAGE FORMS AND STRENGTHS* (3).

409

## 410 12 CLINICAL PHARMACOLOGY

### 411 12.1 Mechanism of Action

412 Upon mixing Sealer Protein (Human) and Thrombin (Human), the two components mimic the final stage of the  
413 blood coagulation cascade. Soluble fibrinogen is transformed into fibrin that adheres to the wound surface and  
414 to the skin flap or graft to be affixed. Due to the low thrombin concentration, initial polymerization of ARTISS  
415 will take up to 60 seconds. The fibrin clot continues to strengthen for up to 2 hours after application.

416

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

421

### 422 12.2 Pharmacodynamics

423 Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into  
424 fibrin (*see Pharmacokinetics* (12.3)).

425

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

432

### 433 12.3 Pharmacokinetics

434 Pharmacokinetic studies were not conducted. Because ARTISS is applied only topically, systemic exposure or  
435 distribution to other organs or tissues is not expected.

436

## 437 **13 NONCLINICAL TOXICOLOGY**

### 438 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

441

## 442 **14 CLINICAL STUDIES**

### 443 **14.1 Burns (grafts)**

444 ARTISS was investigated for adherence of split thickness sheet skin grafts in burn patients in a prospective,  
445 randomized, controlled, evaluator-blinded, multicenter clinical study. In each of the 138 patients, two  
446 comparable test sites were identified after burn wound excision. Skin grafts were adhered at one test site using  
447 ARTISS, and at the other test site using staples (control). The study product was applied once to the wound bed  
448 of the allocated test site during skin grafting surgery.

449

450 The mean  $\pm$  SD estimated total body surface area (TBSA) for all burn wounds was  $13.6 \pm 9.2\%$ . The mean  $\pm$   
451 SD estimated TBSA requiring skin grafting was  $8.0 \pm 6.9\%$ . The mean  $\pm$  SD estimated TBSA for ARTISS test  
452 sites was  $1.7 \pm 0.8\%$  and for the stapled test sites was  $1.7 \pm 0.7\%$ . Burn wound thickness was classified as full  
453 thickness in 106 (76.8%) of the 138 treated subjects, and partial thickness in 32 (23.2%) subjects.

454

455 The safety population contained all 138 treated subjects; however, 11 subjects did not have an available primary  
456 endpoint assessment, leaving a modified intent-to-treat (ITT) set of 127 patients. Complete wound closure by  
457 Day 28 was achieved in 43.3% of the ARTISS test sites and 37.0% of the stapled test sites in the 127 ITT  
458 patients. Wound closure at Day 28 was complete at 72% of the ARTISS and staples test sites for the 1-6 years  
459 old group (N=18), at 32% of the ARTISS test sites and 26% of the staples test sites for the 7-18 years old group  
460 (N=19) and at 40% of the ARTISS test sites and 32% of the staples test sites for the greater than 18 years old  
461 group [ITT]. The lower limit of the 97.5% confidence interval of the difference between ARTISS and staples  
462 was  $-0.029$ . A similar result was obtained in the per protocol (PP) population: complete wound closure by Day  
463 28 was achieved in 45.3% of the ARTISS test sites and 39.6% of the stapled test sites in the 106 PP patients.  
464 The lower limit of the 97.5% confidence interval of the difference between ARTISS and staples was  $-0.041$ .  
465 Therefore, ARTISS was found to be non-inferior to staples in the ITT and PP populations at the 97.5% one-  
466 sided level for complete wound closure by Day 28 because the lower limit of the confidence interval of the  
467 difference between ARTISS and staples success rates was greater than the predefined limit of  $-0.1$ .

468

### 469 **14.2 Facial Rhytidectomy (flaps)**

470 ARTISS was investigated for adherence of skin flaps in facial rhytidectomy surgeries during two prospective,  
471 randomized, controlled, multicenter clinical studies. Both the preliminary study investigating 45 subjects and  
472 the confirmatory study with 75 subjects had a split-face design in which 1 side of the face was treated with  
473 ARTISS as an adjunct to the standard of care (SoC) and the other side received SoC only, which was closure of  
474 the flap by means of staples and suturing only; therefore each subject participated in both arms (ARTISS and  
475 SoC).

476

477 Primary endpoint of the confirmatory study conducted in 75 subjects was the total drainage volume collected  
478 from each side of the face at 24 h ( $\pm 4$  h) post surgery. Occurrence of hematoma and seroma on each side of the  
479 face, comparison of edema between the 2 sides of the face, changes in skin sensitivity from baseline on each  
480 side of the face and subject preference were evaluated as secondary endpoints.

481

482 In both studies, a standardized drain was placed in each side of the face prior to the flap closure and drainage  
483 volume from both sides of the face from all subjects was compared. Pressure dressings were not allowed.

484  
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487

The results for the primary endpoint of the confirmatory study are presented in Table 4a below.

**Table 4a.**

<b>Drainage Volume Comparison at 24 h Post Operative in Confirmatory Study</b>			
<b>Clinical Study (n= 75)</b>	<b>Mean ± SD Drainage (mL) ARTISS Side of the Face</b>	<b>Mean ± SD Drainage (mL) SoC Side of the Face</b>	<b>p-Value</b>
Confirmatory study	7.7 ± 7.4	20.0 ± 11.3	< 0.0001

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A statistically significant difference in drainage volumes was observed, favoring the side of the face treated with ARTISS.

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Drainage volumes at 24 h post operatively for each side of the face reported as secondary endpoint in the preliminary study are presented in Table 4b below.

**Table 4b.**

<b>Drainage Volume Comparison at 24 h Post Operative in Preliminary Study</b>		
<b>Clinical Study (n = 45)</b>	<b>Mean ± SD Drainage (mL) ARTISS Side of the Face</b>	<b>Mean ± SD Drainage (mL) SoC Side of the Face</b>
Preliminary study	11.5 ± 13.7	26.8 ± 24.0

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499  
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501

An integrated analysis of the occurrence of hematoma/seroma in all 120 subjects across two studies was performed. A comparison of the proportion of subjects experiencing a hematoma/seroma exclusively on the ARTISS-treated side or on the SoC side of the face is presented in Table 5 below.

**Table 5.**

<b>Occurrence of Hematoma / Seroma</b>				
<b>Clinical Study</b>	<b>ARTISS n (%)</b>	<b>SoC n (%)</b>	<b>Both Sides of Face n (%)</b>	<b>Total n (%)</b>
Preliminary study	0	9 (20%)	0	9 (20%)
Confirmatory study	2 (2.7%)	5 (6.7%)	3 (4%)	10 (13.3%)

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505

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

ARTISS is supplied in the following pack sizes and presentations:

**Table 6.**

<b>Pack Size</b>	<b>NDC Number</b>		
	<b>ARTISS Kit (Freeze-Dried)</b>	<b>ARTISS Kit (Freeze-Dried) with DUPLOJECT System</b>	<b>ARTISS Pre-Filled Syringe (Frozen) with DUO Set</b>
2 mL	0944-4351-03	0944-4351-04	0944-8503-02
4 mL	0944-4351-07	0944-4351-08	0944-8503-04
10 mL	0944-4351-11	0944-4351-12	0944-8503-10

See *DOSAGE FORMS AND STRENGTHS* (3).

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508

### **Storage**

Store ARTISS in original carton to protect from light. Do not use after the expiration date. Discard if packaging of any components is damaged.

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512

### **ARTISS Kit (Freeze-Dried)**

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

Reconstituted solutions must not be refrigerated or frozen.

515

516 **ARTISS Pre-filled Syringe (Frozen)**

517 Long term: Store at  $\leq -20^{\circ}\text{C}$ .

518 Short term: Room Temperature Thawing: Unopened pouches, thawed at room temperature, may be stored  
519 for up to 14 days at room temperature ( $15-25^{\circ}\text{C}$ ) after removal from the freezer.

520 Quick Thawing: Maintain the product at  $33-37^{\circ}\text{C}$  until use. If the product is removed from  
521 original pouch or warmed to  $33-37^{\circ}\text{C}$  it must be used within 12 hours.

522

523 **Do not refrigerate or re-freeze after thawing. Do not microwave.**

524

525 **17 PATIENT COUNSELING INFORMATION**

526 Inform patients that ARTISS is made from human plasma and discuss the risks and benefits with the patient.

527

528 Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with  
529 immunodeficiency or increased red blood cell turnover. Instruct patients to consult their physician if symptoms  
530 of B19 virus infection appear (fever, drowsiness, chills and runny nose followed about two weeks later by a rash  
531 and joint pain (*see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)*)).

532

533 **Baxter Healthcare Corporation**

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535 US License No. 140

536

537 This product is covered under US Patent Nos. 5,962,405 and 6,579,537.

538

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