VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Fibrin sealants or “fibrin glues” are used to help close and heal wounds. The goal of fibrin glue is to help wounds heal so that sutures and staples will not be needed as much, if at all.

During surgery, sutures and staples are most commonly used for closing a wound. However, there are some downsides to sutures and staples. For example, the sutures or staples may not always be placed in the right spot, they can cause pain, and they can cause scarring. Fibrin glues, such as ARTISS, may be a better option in some cases. Fibrin glues can also be used with staples or sutures. Using fibrin glues alone or together with staples and sutures may be faster, less painful, and lessen the potential for scarring.

ARTISS is a type of low concentration fibrin glue. ARTISS may be used to:

- Help heal and join tissues in cosmetic surgery, reconstructive surgery, and burn surgery,
- Replace and/or support the use of sutures and staples in surgery,
- Help stop bleeding on surfaces just under the skin
There are about 54,000 burn surgeries performed every year. There are about about 1.5 million people every year suffer from burns that require treatment; half of these are from flame burns (Orgill, 2009; Becker & Stucchi, 2006). The number of people worldwide who experience fire-related burn injuries is about 1.1 per 100,000 population (WHO, 2008). The incidence of burns in low and moderate income countries is 1.3 per 100,000 population compared with an incidence of 0.14 per 100,000 population in high income countries (WHO, 2008).

According to the International Society of Aesthetic Plastic Surgery (ISAPS), there were approximately 3,980,135 total plastic surgery procedures in Europe in 2010. About 10% of these procedures were reported to be facial surgical procedures.

Fibrin glues are known to be a good treatment to help stop bleeding, and to help heal wounds. The goals of fibrin glues are to have wounds that are healed well, with less pain and in less time. Although staples and sutures are more of a traditional method, surgeons and doctors must think about the downsides to staples and sutures such as pain, scarring and putting the sutures or staples in the right place. Sometimes, without fibrin glues, patients may take longer to heal and recover from surgery.

VI.2.2 Summary of treatment benefits

As said before, the greatest benefits of using fibrin glue during surgery are to help stop bleeding, help close wounds, and help encourage tissues to heal.

VI.2.3 Unknowns relating to treatment benefits

Fibrin glues have been tested on many people in different age groups and of different races and ethnicities. Most of the people studied were Caucasian. Hispanic, Black, Asian, and Native American people were also studied, but not as much. It is likely that fibrin glues work well in people of all races and ethnicities. Also, many people have had good results with fibrin glues now that the product has been tested and is being used in hospitals.

VI.2.4 Summary of safety concerns

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>ARTISS can cause allergic reactions. If ARTISS is accidentally put in a vein, the chances of having an allergic reaction.</td>
<td>If you’ve had an allergic reaction to a fibrin glue, then you should not get a fibrin glue again. Ask your doctor about medicine to</td>
</tr>
</tbody>
</table>
reaction may increase. There have been reports of allergic reactions to ARTISS. Rarely, these allergic reactions have resulted in death.

prevent an allergic reaction if you have experienced an allergic reaction in the past.

If you have an allergic reaction to this medicine, make sure your nurse or doctor makes a note of it in your medical records.

If you have an allergic reaction, the doctor or surgeon should remove the medicine from the skin or wound right away.

Make sure your doctor tells you about potential allergic reactions with ARTISS such as hives, itching, rash, tightness of the chest, wheezing, and low blood pressure.

Blood clots may form and dislodge to another place in the body due to accidentally injecting the medicine in a vein (Thromboembolic events due to inadvertent intravascular application)

There have been reports with ARTISS of blood clots forming due to the healthcare professional accidentally injecting the medicine into a vein. If this happens, it may be life-threatening.

Healthcare professionals are warned of never applying ARTISS into a vessel

The medicine may not work if it is not handled properly, especially if only a small amount of the medicine is used (Lack of efficacy in small volume use due to drug administration error)

In surgeries that only use a small amount of the medicine, to the doctor should get rid of the first few drops before using ARTISS to make sure the medicine is properly mixed.

Reports have been received of ARTISS not working because the healthcare professional did not get rid of the first few drops coming out of the syringe. Most of these surgeries were eye surgeries.

The first few drops of ARTISS should be discarded from the syringe before using it.

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection from use of the medicine</td>
<td>Fibrin glues are made from products from humans (human plasma). All human plasma goes through a very thorough screening process. However, the potential for getting an infection is never completely gone.</td>
</tr>
</tbody>
</table>

Important potential risks
Too much tissue or scarring may form if too much medicine is used at the site (Granulation tissue formation due to application of excess product)

ARTISS should only be used in a thin layer. If ARTISS is put on too thickly, too much tissue may form or scarring may occur, which may interfere with the medicine’s ability to work and the body’s ability to heal properly.

Spraying air or gas from the spray machine may result in air or gas bubbles forming in the bloodstream if the spray device is used incorrectly (Risk of air or gas embolism, tissue rupture, and air or gas entrapment with the use of spray devices at higher than recommended pressures and in close proximity to the tissue surface)

Surgeons should follow the directions for use for the spray machine. Surgeons should not use too much pressure or spray at too close a distance, because doing so could cause air or gas bubbles in the bloodstream.

ARTISS may react or interfere with other medicines (Interaction/incomaptibility with other medicinal products)

Certain other medicines may react or interfere with ARTISS. Specifically, some medicines that are used to clean the body before surgery have alcohol in them, which may cause ARTISS to not work.

### Important missing information

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>No animal studies on side effects with moderate or long-term use, ability to cause cancer, effects on pregnancy or the fetus, or effect on the immune system have been done. (Preclinical data regarding subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity, or immune stimulation)</td>
<td>No animal studies on side effects after long term use have been performed. No animal studies on pregnant or lactating females have been performed. ARTISS is not recommended for pregnant or lactating females.</td>
</tr>
<tr>
<td>Lack of clinical data on use in human pregnancy or lactation</td>
<td>The safety of fibrin sealants for use in human pregnancy or lactation has not been established in controlled clinical trials.</td>
</tr>
</tbody>
</table>
VI.2.5 Summary of additional risk minimization measures by safety concern

These additional risk minimization measures are for the following risk:

**Risk of air or gas embolism, tissue rupture, and air or gas entrapment with the use of spray devices at higher than recommended pressures and in close proximity to the tissue surface**

**Risk minimization measure(s):** To inform healthcare professionals of risk of air or gas embolism, tissue rupture, and air or gas entrapment with the use of spray devices when used at too high pressure and too short distance. Retrain Baxter sales staff on the correct use, and retrain healthcare professionals on the correct use.

**Objective and rationale:** The objectives of the activities described below are to provide awareness of the risks associated with use fibrin sealant use, prevent harm to patients, ensure that users are properly trained on the use of fibrin sealants, and ensure proper use of Baxter’s fibrin sealants.

**Main additional risk minimization measures:**

- Activity 1: Direct Healthcare Professional Communication letter
- Activity 2: Use of a tag/label to be put on pressure regulators with a symbol that informs about the correct pressure and distance to be used
- Activity 3: Redesign the EasySpray pressure regulator to reduce the maximum pressure delivered.
- Activity 4: Update educational materials for healthcare professionals and internal Baxter personnel
- Activity 5: Training for healthcare professionals
- Activity 6: Training for internal personnel at Baxter
- Activity 7: Create educational website

VI.2.6 Planned post-authorization development plan

There are no post-authorization studies planned for ARTISS.

**Studies which are a condition of the marketing authorization**

There are no studies planned that are a condition of marketing authorization for ARTISS.

VI.2.7 Summary of changes to the Risk Management Plan over time

A table of the changes that have occurred with the Risk Management Plan for ARTISS is provided below.

**Major changes to the Risk Management Plan over time**

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Safety concerns</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>18 January 2008</td>
<td>• The potential risk</td>
<td>None</td>
</tr>
</tbody>
</table>
Risk Management Plan Version 2.0

<table>
<thead>
<tr>
<th>3.0</th>
<th>10 August 2009</th>
<th>No updates.</th>
<th>Included results of study 550703.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>18 January 2012</td>
<td>The risk of “intravascular application” was amended to “thromboembolic events due to inadvertent intravascular application”.</td>
<td>RMP updated to align with the CCSI which contained the latest wording on the air/gas embolism warning. Included results of study 550901.</td>
</tr>
<tr>
<td>Version</td>
<td>Date</td>
<td>Changes and Updates</td>
<td></td>
</tr>
<tr>
<td>---------</td>
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<td>-------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>18 January 2012</td>
<td>- The identified risk of “lack of efficacy in small volume use due to drug administration error” was added. Submitted as part of a commitment to AGES to provide an updated RMP with the next PSUR. Also includes results of study 550902.</td>
<td></td>
</tr>
</tbody>
</table>
| 1.0 (First version under new GVP, combined with TISSEEL and ARTISS) | Q1/2013 | No new safety concerns.  
- The risk of “air embolism, tissue rupture, or gas entrapment with the use of spray devices” was amended to “air or gas embolism, tissue rupture, and air or gas entrapment with the use of spray devices at higher than recommended pressures and in close proximity to the tissue surface” for greater clarity.  
Version 1.0 update following PVAR:  
- Inclusion of additional risk minimization activities as additional pharmacovigilance for the risk of air or gas embolism  
- Added the following as Missing Information: *Lack of clinical data on use in human pregnancy or lactation.*  
Submitted to national competent health care authorities in countries where TISSEEL and/or TISSUCOL and/or ARTISS are licensed, following the Referral under Article 31 regarding air or gas embolism with fibrin sealants with spray devices (EMEA/H/A-31/1337)  
Procedure number AT/H/0317/001-002/IB/026 |
| 2.0     | Q4/2013    | No change to safety concerns since the last version was submitted.                                                             |