TISSEEL, TISSUCOL, AND ARTISS
Risk Management Plan

Version 3.0
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TISSEEL

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Surgical conditions represent a major source of disease burden globally. In Europe, there are about 500,000 heart surgeries done every year that may require medicine to stop bleeding. It is also estimated that there are approximately 2.5 million surgeries on the gut every year, with 48% of those surgeries being to remove a part of the gut. There are also 2.1 million brain or spinal surgeries done every year, which may also include surgeries to stop spinal fluid leaking from the spin, nose, throat or eye.

During such surgeries, fibrin sealants or 'fibrin glue' may be 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. Using fibrin glue alone or together with staples and sutures may provide a beneficial option during surgery to help wounds heal well, with less pain and in less time. TISSEEL is a type of highly concentrated fibrin glue. TISSEEL may be used to:

- Help stop bleeding in surgery
- Help wounds heal (with or without sutures) in surgery of:
    - The vascular system (the veins or tubes that carry the blood),
    - The joining of the stomach or intestines back together,
    - The spine or brain where there is contact with spinal fluid or the outer layer of the brain/spine (for example, surgery on the ears, nose, throat, eyes, or spine),[13]
- Help tissue sealing, to help two pieces of skin stay together or to help attach a new piece of skin to an area where there is missing skin.

There are about 1.2 million heart surgeries done every year that may require medicine to stop bleeding. It is also estimated that there are 2.5 million surgeries on the gut every year, with 48% of those surgeries being to remove a part of the gut. There are also 2.1 million brain or spinal surgeries done every year, including surgeries to stop fluid leaking from the spine in ear, nose, throat, eye, and spinal surgeries.[14]

VI.2.2 Summary of Treatment Benefits

During surgery, sutures and staples are most commonly used for closing a wound. 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.

[13] [14] In the EU, TISSEEL is licensed either nationally or via an MRP. In the case of national licenses, the indications are different in various countries. The indication "As a tissue glue to improve wound healing or to support sutures in Neurosurgery and surgical interventions where contact with cerebrospinal fluid (CSF) or dura mater may occur (e.g., ENT, ophthalmic, and spinal surgeries)" is not approved in all EU countries.

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. It is likely that fibrin glues work well in people of all races and ethnicities.

VI.2.4 Summary of Safety Concerns

Table 41. Important Identified Risks

Risk	What is known	Preventability
Hypersensitivity	TISSEEL can cause allergic reactions. If TISSEEL is accidentally put in a vein, the chances of having an allergic reaction may increase. There have been reports of allergic reactions to TISSEEL. Rarely these allergic reactions have resulted in death.	If there has been an allergic reaction to a fibrin glue, then fibrin glue should not be used again. Make sure the doctor talks about potential allergic reactions with TISSEEL 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 TISSEEL 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 to never apply TISSEEL 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 the medicine should be properly mixed. Most of these surgeries were eye surgeries.	Healthcare professionals are instructed to discard the first few drops of TISSEEL from the syringe before using it.
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)	The air or gas bubbles seem to be related to use of the spray device at higher than recommended pressure and/or in close distance to the tissue surface.	When using the spray machine, surgeons should use pressure within the proper pressure range and proper distance recommended by the spray device manufacturer.

Table 42. Important Potential Risks

Risk	What is known
Infection from use of the medicine (Risk of transmission of infective agents)	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.
Tissue sealing on undesired sites and too much tissue or scarring may form if too much medicine is used at the site (Tissue adhesion at undesired sites and granulation tissue formation due to application of excess product)	Care must be taken to cover all parts of the body outside the area to be treated to avoid tissue sealing on undesired sites. TISSEEL should only be used in a thin layer. If TISSEEL 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.
TISSEEL could be used improperly in hernia repair surgeries (Suboptimal application technique during hernia repair)	It is important that whenever TISSEEL is used, the dose is chosen based on the type of procedure, size of the area, way of applying the medicine (spray or non-spray), and how much is needed.
TISSEEL may react or interfere with other medicines (Interaction/incompatibility with other medicinal products)	Certain other medicines may react or interfere with TISSEEL. Specifically, some medicines that are used to clean the body before surgery contain alcohol, which may cause TISSEEL to not work.

Table 43. Missing information

Risk	What is known
No animal studies on the 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)	No animal studies on effects after long-term use have been performed. No animal studies on pregnant females have been performed. TISSEEL is not recommended for pregnant females.
Lack of clinical data on use in human pregnancy or lactation	The safety of fibrin sealants for use in human pregnancy or breastfeeding has not been established in controlled clinical studies. TISSEEL is not recommended for pregnant or breastfeeding females.
Limited information in pediatric patients	The safety and effectiveness of fibrin sealants for use in pediatric patients has not been well established in controlled clinical studies.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicines, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures).

These additional risk minimization measures are for the following risk:

Table 44. 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 pressure and in close proximity to the tissue surface)

Risk minimization measure(s): Additional risk minimization measures have been implemented to inform healthcare professionals of the risk of air or gas embolism with fibrin sealants with spray devices when used at too high pressure and/or too short distance. Baxter sales staff has been retrained on the correct use, and in turn retrained 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 of the EasySpray pressure regulator to reduce the maximum pressure delivered. • Activity 4: Creation of educational materials for healthcare professionals and internal Baxter personnel • Activity 5: Training program for HCPs • Activity 6: Training program for internal Baxter • Activity 7: Educational website on correct use of product with spray application

VI.2.6. Planned Post-Authorization Development Plan

There are no post-authorization safety studies planned for TISSEEL.

Studies which are a Condition of the Marketing Authorization

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

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 TISSEEL is provided below.

Major Changes to the Risk Management Plan Over Time

Table 45. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
2.0	31 MAY 2009	• The risk of "intravascular application" was amended to "thromboembolic events due to inadvertent intravascular application". • "Medication errors" was added as a potential risk to describe the risk of lack of effect if the first few drops of TISSEEL are not expelled. • The potential risk "granulation tissue formation, residual fibrin, inflammation and foreign body reaction as well as skin induration" was added. • The missing information "Interaction with other medicinal products; Incompatibilities" was added. • The missing information "Preclinical studies regarding subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation" was added.	None

Table 45. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
3.0	13 DEC 2010	• The RMP was updated to include the "risk of air embolism, tissue rupture, and gas entrapment with compression with the use of spray devices". • The potential risk of "suboptimal application technique during hernia repair" was added.	RMP updated in response to the day 59 questions on the CCSI update, which contained the latest wording on the air/gas embolism warning.
4.0	18 JAN 2012	• No new safety concerns. • The risk of "interaction/incompatibility with other medicinal products" was changed from missing information to a potential risk per the definitions of missing information and potential risks. • The risk of "medication errors" was amended to "lack of efficacy in small volume use due to drug administration error" and changed from a potential risk to an identified risk because Baxter received reports of this (although there was no signal).	Submitted as part of a commitment to AGES to provide an updated RMP with the next PSUR. Also included results of study 550801 and 550904.
1.0 (First version under new GVP, combined with TISSUCOL and ARTISS)	Q1/2013	• No new safety concerns. • The potential risk of "air embolism, tissue rupture, and gas entrapment with compression with the use of spray devices" was amended to "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" for greater clarity.	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

Table 45. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		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".	
2.0	Q4/2013	No change to safety concerns since the last version was submitted.	• Adaptions in response to specific MoH requests: Update in response to questions from Ireland MoH, dated 13 SEP 2013 • Update in response to request for commitment from Finland MoH to modify version 1.0 of the RMP as follows: Section VI.2.4 Summary of Safety concerns – to modify the current wording "Your doctor should be very careful not to inject TISSEEL into any tissue." to a more precise wording. • Reflect the situation that the indication "As a tissue glue to improve wound healing or to support sutures in Neurosurgery and surgical interventions where contact with cerebrospinal fluid (CSF) or dura mater may occur (e.g., ENT, ophthalmic, and spinal surgeries)" is not approved in all EU countries for TISSEEL.

Table 45. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
3.0	Q4 2015	'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' was re-categorized from an important potential risk to an important identified risk per GPV Definitions. Completed additional risk minimization measures as follows: • DHPC • 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 • Redesign of the EasySpray pressure regulator to reduce the maximum pressure delivered • Creation of educational materials and instructions for use for HCPs and internal Baxter personnel • Training program for HCPs • Training program for internal Baxter personnel • Educational website on correct use of product with spray application Version 3.0 update following PVAR: • The important identified risk of 'Allergic reactions' has been revised to 'Hypersensitivity' • The important potential risk of 'Granulation tissue formation due to application of excess product' has been revised to 'Tissue adhesion	RMP updated to reflect that additional risk minimizations were fulfilled.

Table 45. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		at undesired sites and granulation tissue formation due to application of excess product'. • Addition of missing information, 'Limited information in pediatric patients' (TISSEEL and TISSSUCOL)	

ARTISS

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Surgical conditions represent a major source of disease burden globally. In Europe, there are about 500,000 heart surgeries done every year that may require medicine to stop bleeding. It is also estimated that there are approximately 3.9 million total plastic surgery procedures in Europe in 2010 and about 10% of these procedure were reported to be facial surgical procedures. The population that may use ARTISS will vary based on medical condition, however for ARTISS use with burns, the population is commonly young adult males and children.

During such surgeries, fibrin sealants or "fibrin glue" may be used to help close and seal wounds. The goal of fibrin glue is to help tissue to adhere or seal tissue and help stop bleeding.

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

About 54,000 burn surgeries are performed every year. There are about 1.5 million people every year who suffer from burns that require treatment; half of these are from flame burns. The number of people worldwide who experience fire-related burn injuries is about 1.1 per 100,000 persons. The incidence of burns in low and moderate income countries is 1.3 per 100,000 persons compared with an incidence of 0.14 per 100,000 persons in high income countries.

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.

VI.2.2 Summary of Treatment Benefits

During surgery, sutures and staples are most commonly used for closing a wound. 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.

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.

VI.2.4 Summary of Safety Concerns

Table 55. Important Identified Risks

Risk	What is known	Preventability
Hypersensitivity	ARTISS can cause allergic reactions. If ARTISS is accidentally put in a vein, the chances of having an allergic reaction may increase. There have been reports of allergic reactions to ARTISS. Rarely, these allergic reactions have resulted in death.	If there has been an allergic reaction to a fibrin glue, then fibrin glue should not be used again. Make sure the doctor talks 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 to never apply 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, the medicine should be properly mixed. Most of these surgeries were eye surgeries.	Healthcare professionals are instructed to discard the first few drops of ARTISS from the syringe before using it.
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)	The air or gas bubbles seem to be related to use of the spray device at higher than recommended pressure and/or in close distance to the tissue surface	When using the using the spray machine, surgeons should use pressure within the proper pressure range and proper distance recommended by the spray device manufacturer.

Table 56. Important Potential Risks

Risk	What is known
Infection from use of the medicine (Risk of transmission of infective agents)	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.
Tissue sealing on undesired sites and too much tissue or scarring may form if too much medicine is used at the site (Tissue adhesion at undesired sites and granulation tissue formation due to application of excess product)	Care must be taken to cover all parts of the body outside the area to be treated to avoid sealing on undesired sites. 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.
ARTISS may react or interfere with other medicines (Interaction/incompatibility 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 contain alcohol, which may cause ARTISS to not work.

Table 57. Missing Information

Risk	What is known
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)	No animal studies on side effects after long term use have been performed. No animal studies on pregnant females have been performed. ARTISS is not recommended for pregnant females.
Lack of clinical data on use in human pregnancy or lactation	The safety of fibrin sealants for use in human pregnancy or lactation has not been established in controlled clinical studies. ARTISS is not recommended for pregnant or breastfeeding females.

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the

medicines, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures).

These additional risk minimization measures are for the following risk:

Table 58. Spraying air or gas from the spray machine may result in air or gas bubbles forming in the blood stream 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 pressure and in close proximity to the tissue surface)

Risk minimization measure(s): Additional risk minimization measures have been implemented to inform healthcare professionals of the risk of air or gas embolism, with fibrin sealants with spray devices when used at too high pressure and/or too short distance. Baxter sales staff has been retrained on the correct use, and in turn retrained 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 of the EasySpray pressure regulator to reduce the maximum pressure delivered. • Activity 4: Creation of educational materials for healthcare professionals and internal Baxter personnel • Activity 5: Training program for HCPs • Activity 6: Training program for internal personnel at Baxter • Activity 7: Educational website on correct use of product with spray application

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.

Table 59. Major changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
2.0	18 JAN 2008	• The potential risk "granulation tissue formation, residual fibrin, inflammation and foreign body reaction as well as skin induration" was added. • The missing information "interaction with other medicinal products; incompatibilities" was added. • The missing information "preclinical studies regarding subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation" was added. • "Medication errors" was added as a potential risk to describe the risk of lack of effect if the first few drops of ARTISS are not expelled.	None
3.0	10 AUG 2009	No changes to the safety concerns.	Included results of study 550703.
4.0	18 JAN 2012	• The risk of "intravascular application" was amended to "thromboembolic events due to inadvertent intravascular application". • The identified risk of "lack of efficacy due to drug administration error" was added. • The potential risk of "air embolism, tissue rupture, and gas entrapment with the use of spray devices" was added. • The risk of "interaction/incompatibility with other medicinal products" was changed from missing	RMP updated to align with the CCSI which contained the latest wording on the air/gas embolism warning. Included results of study 550901.

Table 59. Major changes to the Risk Management Plan over time

		information to a potential risk per the definitions of missing information and potential risks.	
5.0	18 JAN 2012	• 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.
1.0 (First version under new GVP, combined with TISSEEL, TISSUCOL, and ARTISS)	Q1/2013	No new safety concerns. • The potential 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)
2.0	Q4/2013	No change to safety concerns since the last version was submitted.	Adaptions in response to specific MoH requests: • Update in response to questions from Ireland MoH, dated 13 Sept 2013
3.0	Q4 2015	'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' was re-categorized from an important potential risk to an important identified risk per GVP Definitions. Completed additional risk	RMP updated to reflect that additional risk minimizations were fulfilled.

Table 59. Major changes to the Risk Management Plan over time

		minimization measures as follows: • DHPC • 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 • Redesign of the EasySpray pressure regulator to reduce the maximum pressure delivered • Creation of educational materials and instructions for use for HCPs and internal Baxter personnel • Training program for HCPs • Training program for internal Baxter personnel • Educational website on correct use of product with spray application Version 3.0 update following PVAR: • The important identified risk of 'Allergic reactions' has been revised to 'Hypersensitivity' • The important potential risk of 'Granulation tissue formation due to application of excess product' has been revised to 'Tissue adhesion at undesired sites and granulation tissue formation due to application of excess product'.	