



Dear Customer,

Baxter Healthcare is providing you with the following information to advance the safe and appropriate use of our products. Therefore, the purpose of this letter is to clarify some important issues related to *fibrin sealants*. Specifically, this document will address:

1. The difference between the fibrin sealant product category and the FDA approved indication(s).
2. Ingredients used to provide clot stability.

FIBRIN SEALANT CLASS

Currently there are 3 *fibrin sealants* approved in the US. Approved fibrin sealants are either indicated as adjuncts to hemostasis, or tissue sealants, or both¹. Additionally, a fibrin sealant has been approved for adherence of autologous skin grafts resulting from burns.

A hemostasis indication may be either general, meaning as an adjunct to hemostasis in nonspecified surgeries, or specific to a surgical procedure or area of the body. While the established, or proper name of this product category contains the word “sealant”, **this does not necessarily mean the product is FDA approved for use in tissue sealing**. It is important to note that sealing and hemostasis indications are different. Products are granted indications for use by the FDA following Agency review of clinical safety and efficacy data in pivotal clinical trials evaluating a prespecified endpoint (e.g., hemostasis or tissue sealing). A fibrin sealant must be evaluated in one or more pivotal clinical trials before an indication is granted by the FDA for use as an adjunct to achieving hemostasis, as a sealant, or both.

TISSEEL indications are as follows:

- **Hemostasis: TISSEEL is indicated** for use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligation and cautery, is ineffective or impractical. TISSEEL is a satisfactory hemostatic agent in fully heparinized patients undergoing cardiopulmonary bypass.
- **Sealing: TISSEEL is indicated** as an adjunct to prevent leakage from colonic anastomoses following the reversal of temporary colostomies.

ARTISS indication is as follows:

- ARTISS is indicated to adhere autologous skin grafts to surgically prepared wound beds resulting from burns in adult and pediatric populations. ARTISS is not indicated for hemostasis.

Of the three fibrin sealants licensed in the US today, TISSEEL is the only one with a sealing indication and ARTISS is the only one approved for adherence of autologous skin grafts resulting from burns.

CLOT STABILITY

Commercially produced fibrin sealants are composed of purified, virus-inactivated/removed human fibrinogen and human thrombin, with or without added components such as virus-inactivated/removed human factor XIII and/or aprotinin¹. Thus, a fibrin sealant may contain an antifibrinolytic agent to preclude premature clot lysis and to extend the durability of the clot when fibrinolysis or hyperfibrinolytic surgical situations (e.g., surgeries involving cardiopulmonary bypass and trauma) might accelerate the breakdown of fibrin clot.

TISSEEL and ARTISS contain minimal amounts of synthetic aprotinin (2250 – 3750 KIU/mL) to effectively delay fibrinolysis. In pre-clinical studies, the addition of aprotinin was demonstrated to improve clot persistence.

Fibrin Sealants are made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Baxter places the health and well being of our patients primary to all aspects of our business, and as such we believe that reiterating and clarifying the appropriate indications are the most responsible way to ensure product efficacy and utility. Similarly, we believe the addition of an antifibrinolytic agent is an important component to extend the durability of the clot in surgical situations.

For complete prescribing information, please refer to the enclosed TISSEEL and ARTISS prescribing information. If you would like additional information, please contact Baxter medical information at 1-800-424-6724 or your local sales representative.

Sincerely,

Dr. Mark Bechter, BM
Medical Director, BioSurgery
Baxter Healthcare Corporation
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USA

Enclosures:
TISSEEL Prescribing Information
ARTISS Prescribing Information

Reference:

1. FDA Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use.

Please see Important Risk Information for ARTISS and TISSEEL on pages 3 and 4 and accompanying full Prescribing Information.

TISSEEL [Fibrin Sealant] Indications

Hemostasis: TISSEEL is a fibrin sealant indicated as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries. TISSEEL is satisfactory for use in fully heparinized patients undergoing cardiopulmonary bypass

Sealing: TISSEEL is indicated as an adjunct to prevent leakage from colonic anastomoses following the reversal of temporary colostomies

Important Risk Information for TISSEEL

For Topical Use Only. Do not inject TISSEEL directly into the circulatory system. Intravascular application of TISSEEL may result in life-threatening thromboembolic events. Caution should be exercised to minimize any risk of inadvertent intravascular application.

Do not use TISSEEL in individuals with a known hypersensitivity to aprotinin.

Do not use TISSEEL for the treatment of severe or brisk arterial bleeding. In these situations, TISSEEL will be washed away in the flow of blood before hemostasis can be attained.

Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of TISSEEL. Symptoms associated with allergic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock. Such reactions may also occur in patients receiving TISSEEL for the first time.

Discontinue administration of TISSEEL in the event of hypersensitivity reactions.

Apply as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

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 use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

When applying fibrin sealants using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer.

Exposure to solutions containing alcohol, iodine or heavy metals may cause TISSEEL to be denatured. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before the application of TISSEEL.

The safety and effectiveness of TISSEEL used alone or in combination with biocompatible carriers in neurosurgical procedures or other surgeries involving confined spaces have not been evaluated; its use in this setting is not FDA approved.

There have been rare reports of serious adverse events such as paralysis and other compressive complications possibly related to the use of fibrin sealant in combination with resorbable hemostatic agents.

TISSEEL is made from human plasma. It may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Please see accompanying full Prescribing Information.

ARTISS [Fibrin Sealant (Human)] Indication

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

ARTISS is not indicated for hemostasis.

Important Risk Information for ARTISS

For Topical Use Only. Do not inject ARTISS directly into blood vessels. Intravascular application of ARTISS may result in life-threatening thromboembolic events.

Do not use ARTISS in individuals with a known hypersensitivity to aprotinin and/or hypersensitivity to any of the active or excipients.

Hypersensitivity or allergic/anaphylactoid reactions may occur with the use of ARTISS. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock. Such reactions may also occur in patients receiving ARTISS for the first time.

Discontinue administration of ARTISS in the event of hypersensitivity reactions.

Apply as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Air or gas embolism has occurred with the use of spray devices employing a 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 tissue surface.

When applying ARTISS using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer.

Exposure to solutions containing alcohol, iodine or heavy metals may cause ARTISS to be denatured. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before the application of ARTISS and made as dry as possible.

ARTISS is made from human plasma. It may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Adverse reactions occurring in greater than 1% of patients treated with ARTISS were skin graft failure (5 events of 138 patients treated) and pruritus (2 events of 138 patients treated).

Please see accompanying full Prescribing Information.