TISSEEL
[Fibrin Sealant]

TISSEEL/TISSUCOL Fibrin Sealant

Global Value Dossier

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Confidential

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Executive Summary

Surgery comes with various risks, some minor and some life-threatening. Fibrin sealants have proven value in reducing some of these risks which include, but are not limited to, blood loss and resultant transfusion needs, leakage and drainage output, seroma formation, and post-operative patient recovery pain and disability.

Foremost, effectively achieving and maintaining hemostasis intraoperatively and post-operatively is a critical requirement of all surgeries. Failure can result in excessive bleeding, thereby increasing avoidable complications that often lead to longer hospital stays, increased healthcare utilization, and higher healthcare costs. Additionally, blood transfusions are also associated with negative outcomes, including bacterial infection (Blumberg & Heal, 1996; Chelemer, 2002; Goodnough, 1999; Hill, 2003), slower recovery (Koch, 2006), and mortality (Aronson, 2008; Kim, 2007; Murphy, 2007). Studies have shown that hospital length of stay can be 1.5 to 2.5 times longer for patients with impaired hemostasis/transfusion (Stokes, 2011), and these complications are associated with significantly higher healthcare costs (Patel, 2008; Shander, 2010; Stokes, 2011).

Fluid leakage, including cerebrospinal fluid (CSF) leakage, leaking anastomoses, and prophylactic drain volume, also significantly increase morbidity, mortality, and healthcare costs (Elgamal, 2008; Grotenhuis, 2005; Hyman, 2007; Platell, 2005). Other complications such as post-operative pain, seroma formation, and wound dehiscence have significant avoidable financial and clinical implications to patients and payers. The role of fibrin sealants, and TISSEEL in particular, in preventing or reducing complications has been proven via studies conducted over the last 20+ years in multiple countries, surgical settings, and specialities.

TISSEEL/TISSUCOL

TISSEEL Fibrin Sealant is a two-component fibrin sealant matrix (human fibrinogen and human thrombin) which mimics the final stages of the natural clotting cascade by producing a physiologic, biocompatible clot. Once applied, TISSEEL safely and effectively controls diffuse and/or oozing bleeds across broad surfaces and around anastomoses (Lowe, 2007). The mechanism of action does not vary by use, whether for hemostasis, sealing, or tissue adhesion. TISSEEL is regularly used in a supportive capacity in surgeries including cardiovascular procedures, bariatric procedures, hernia repair, general surgery, neurosurgery, and surgical procedures where contact with CSF or dura mater can occur.

Clinical studies demonstrating efficacy and safety of TISSEEL have been conducted in a multitude of treatment modalities, surgical procedures, and at different anatomical locations under different applications techniques, including but not limited to endoscopic/laparoscopic treatment, vascular surgery, gastrointestinal anastomoses, and neurosurgery.

Intraoperative Value of TISSEEL

TISSEEL is an effective alternative for achieving and maintaining hemostasis. Studies in cardiac, cardiovascular, and gynecological surgery comparing TISSEEL with other hemostatic methods have shown a significantly higher rate of successful hemostasis and a shorter time to achieve hemostasis with TISSEEL (Rousou, 1989; Saha, 2011; Saha, 2012; Angioli, 2012). With TISSEEL, significantly fewer patients need blood transfusion and less blood when transfusion is required (Kieser, 1995; Lobato, 2001; Martinelli, 1995; White, 2009).

Other benefits of TISSEEL use have been demonstrated in the literature.

- In neurosurgery, TISSEEL is associated with fewer CSF leaks compared to other dura closure and sellar reconstruction methods (Kassam, 2003; Seiler & Mariani, 2000).
- Studies in multiple surgical areas have shown less anastomosis leakage (Romeo, 1986; Silecchia, 2008) and drainage volume (Gilly, 1998; Maharaj, 2006; Uwiera, 2005; White, 2009; Yeom, 2008).
- Studies in hernia repair and myomectomy have shown shorter operative times with TISSEEL (Angioli, 2012; Benizri, 2006; Negro, 2011; Olmi, 2007).

Post-operative Value of TISSEEL

From a patient perspective, speedy recovery from surgery is paramount and often is associated with greater satisfaction with care. Studies on TISSEEL have demonstrated value in reducing post-operative recovery patient pain and discomfort, thereby returning the patient to normal activity and productivity quicker.

- Most studies demonstrating pain reduction and improved quality of life are in the area of hernia repair (Benizri, 2006; Campanelli, 2012; Ceccarelli, 2008; Fortelny, 2008; Fortelny, 2012; Hidalgo, 2005; Kaul, 2012; Lau, 2005; Lovisetto, 2007; Negro, 2011; Olmi, 2007; Schwab, 2006; Testini, 2010; Topart, 2005).

The literature reports additional post-operative benefits of TISSEEL:

- Studies have reported less seroma formation (Jain, 2004; Lobato, 2001; Maharaj, 2006) and wound dehiscence (Fabrizio, 1995), among other clinical benefits of TISSEEL (Canonico, 1999; Lobato, 2001).
- Studies in hernia repair, spinal surgery, and cancer surgeries have demonstrated shorter hospital lengths of stay for TISSEEL patients (Benizri, 2006; Canonico, 1999; Fabrizio, 1995; Gilly, 1998; Lobato, 2001; Olmi, 2007; Yeom, 2008).
- Pediatric surgery studies have shown TISSEEL patients to have less post-operative bleeding (Huth, 1983; Becker & Willital, 1994), less fluid leakage (Sojo, 2004; Upadhyaya, 2007), and less fistula formation (Becker & Willital, 1994; Gopal, 2008).

VALUE MESSAGES

#1: TISSEEL shows a significantly higher rate of successful hemostasis and a shorter time to hemostasis, compared to other hemostatic methods

#2: TISSEEL use results in significant reductions in healthcare resource utilization, including fewer blood transfusions and shorter operating time

#3: TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity

#4: TISSEEL reduces cost of surgical and post-surgical care

Economic Value

TISSEEL has been reported to reduce avoidable costs in hernia repair, neurosurgery, and other procedures. In the late 1990s, Canonico et al. concluded that the cost of hernia repair with TISSEEL was US$5,600, while without TISSEEL, higher complications lead to prolonged stays averaging US$23,000 (Canonico, 1999). In 2001, Lobato et al. demonstrated complications related to blood transfusion and prolonged hospitalization in hernia repair patients were reduced by US$460 per patient with TISSEEL use (Lobato, 2001).[1] In 2010, Lobato et al. illustrated similar results with estimated avoidable cost of €5462 savings per case (Lobato, 2010). Authors of a large neurosurgery study estimated a total cost savings of at least $75,151 if TISSEEL had been applied to all of study cases (Kassam, 2003).

Budget Impact Models

Three budget impact (BI) models have been developed by Baxter to illustrate the value of TISSEEL. The models are for illustrative purposes only; results may vary in different markets, depending on local treatment practices and costs of medical care in different countries. The three models focus on incisional hernia repair, gastric bypass, and spine surgery. Results demonstrate that:

The cost per incisional hernia repair case with TISSEEL is lower compared to no fibrin sealant. Based on the differences in hospital lengths of stay following the procedure and reductions in blood transfusions, the average cost savings per case with TISSEEL is approximately €5,500.

1 The large cost differences in the Canonico et al. and Lobato et al. study may have multiple explanations. Neither study reported the year in which they were valuing costs. In addition, Canonico et al.'s TISSEEL and control patients were hospitalized, on average, 1 and 7 days, respectively. In the Lobato et al. study, TISSEEL and control patients had much longer average hospitalizations – 7 and 12.6 days, respectively. Furthermore, Canonico et al. studied inguinal hernia repair, while Lobato et al. looked at incisional hernia repair.

The use of TISSEEL in gastric bypass surgery reduces the rate of leaking anastomoses. This reduces the need for diagnostic procedures, re-surgery, and hospital length of stay. The BI model illustrates that use of TISSEEL reduces the cost per gastric bypass surgery by approximately €1,600.

Reducing CSF leaks using TISSEEL offers cost-savings attributed to reduced need for lumbar drain and re-operation. The cost savings achieved per case with TISSEEL compared to no fibrin sealant is approximately US$627 per case.

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Introduction

Complications of surgery can range from minor to life-threatening and can dramatically increase the cost of care; but many, particularly impaired hemostasis, fluid leakage, seroma formation, and post-operative pain, can be minimized with the use of long-acting sealants, namely TISSEEL.[2] With an understanding of how complications impact patient outcomes, readers of this dossier will better understand the value of TISSEEL to healthcare providers, patients, and payers.

TISSEEL Value Proposition

TISSEEL provides value both intra- and post-operatively by reducing blood loss and the need for blood transfusions, preventing fluid leakage and seroma formation, and decreasing post-operative pain. TISSEEL's safety and efficacy in surgery improve clinical outcomes and demonstrate cost-savings. This document provides the scientific evidence supporting the following Value Messages.

INTRAOPERATIVE VALUE

#1: TISSEEL shows a significantly higher rate of successful hemostasis and a shorter time to hemostasis, compared to other hemostatic methods

Studies have shown TISSEEL to be associated with rapid hemostasis times, reduced blood loss volume, and less change in hemoglobin values pre-to-post surgery.

#2: TISSEEL use results in significant reductions in healthcare resource utilization, including fewer blood transfusions and shorter operating time

TISSEEL effectively and rapidly stops surgical bleeding, so fewer patients require blood transfusions. Those who do need transfusion require less blood units compared to other hemostatic agents. Moreover, TISSEEL acts as a sealant for suture lines (anastomoses and dura closures).

POST-OPERATIVE VALUE

#3: TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity

TISSEEL is associated with a reduced risk of leaks and seroma formation, as well as with reduced post-surgical drainage volume. In addition, TISSEEL has demonstrated value reducing post-operative pain and discomfort, thereby reducing analgesic use and returning the patient to normal activity and productivity quicker.

#4: TISSEEL reduces cost of surgical and post-surgical care

Since patients receiving TISSEEL during surgery require less hospital resources and have shorter operation times and hospital lengths of stay, healthcare costs are reduced.

Multiple studies across a wide variety of surgical areas have demonstrated TISSEEL's ability to (1) reduce surgical blood loss and leaks, (2) reduce the need for healthcare resource utilization, (3) reduce pain and improve quality of life, and (4) reduce costs. The results of studies demonstrating TISSEEL's value in these areas are presented throughout this document.

2 In some countries TISSEEL is licensed under the name of TISSUCOL.

TISSEEL Fibrin Sealant

Overview

TISSEEL Fibrin Sealant is a two-component matrix consisting of human fibrinogen and human thrombin, which when mixed together, mimic the final stages of the natural clotting cascade by producing a physiologic, biocompatible clot.[3,4] Specifically, the clotting cascade is initiated by conversion of fibrinogen into fibrin via the enzymatic activities of thrombin and factor XIII. The components included in the TISSEEL package are designed to ensure that physiologic fibrinogenesis is duplicated as closely as possible.

Once applied, TISSEEL safely and effectively controls diffuse and/or oozing bleeds across broad surfaces and around anastomoses (Lowe, 2007). TISSEEL reacts with tissue and forms covalent bonds between fibrin and collagen or fibrin-fibronectin and collagen resulting in hemostasis and tissue sealing. Since collagen is present in one quarter of the body's structural proteins, adequate binding sites for TISSEEL exists in all organs and tissues. Furthermore, the fibrinogen component of TISSEEL contains certain factors, which provide an ideal matrix for cellular in-growth which can aid in wound healing.

A benefit of TISSEEL is that it is naturally reabsorbed by the body as clots are broken down through plasmin-mediated lysis, or fibrinolysis. This biocompatibility, along with adhesive properties and elasticity, contributes to the versatility of TISSEEL as a valuable adjunct to surgical procedures. In addition, a differentiating attribute of TISSEEL compared to other fibrin sealants is that it includes aprotinin which slows the natural fibrinolysis process that occurs around wound sites. This prolongs the stability of TISSEEL clots and prevents premature clot degradation which can result in secondary hemorrhage. Under normal conditions, clots begin to degrade after 1 to 2 days in most tissues. Aprotinin extends the stability of TISSEEL clots for 9 to 10 days.[5] For more information about aprotinin or how TISSEEL compares to other fibrin sealants and hemostatic agents, see Appendix A: Competitive Comparison and Appendix B: The Use of Aprotinin.

TISSEEL is regularly used in a supportive capacity in surgeries including cardiovascular procedures, bariatric procedures, hernia repair, general surgery, neurosurgery, and other surgical procedures where contact with cerebrospinal fluid or dura mater can occur. Depending on the problem being addressed during surgery, application of TISSEEL results in clot formation leading to at least one of three outcomes: hemostasis, sealing, and/or tissue adherence.

- **Hemostasis:** when the product is applied on a large oozing surface of bleeding capillaries (e.g., epicardial tissue, liver or spleen surface), the fibrin clot formation provides a "micro-sealing" of the capillaries, based on the clot adhesion to tissue through a covalent binding between fibrin and collagen or fibrin-fibronectin and collagen.
- **Sealing:** when this covalent binding of the TISSEEL clot occurs on the surface of a hollow organ (blood vessel, gastrointestinal tract, dura mater or bronchial tree, or lymphatic vessel), effective sealing occurs.
- **Tissue Adherence:** when the TISSEEL components are interposed between cut/detached surfaces of an organ or tissue (skin grafts, parenchymal organ cuts, transacted nerves, mesh fixation), adhesion of the tissues occurs.

The mechanism of action of TISSEEL, and all of its licensed variants, is always the same regardless of whether it is used to address hemostasis, sealing, or tissue adherence. Furthermore, TISSEEL's mechanism of action and efficacy do not vary by gender, age, organ, type of surgery, or surgical approach. TISSEEL has been proven effective in patients who have been treated with heparin or those on single or dual anti-platelet therapy.

3 TISSEEL/TISSUCOL [Fibrin sealant] Abbreviated summary of product characteristics; 02/2011.
4 DuraSeal Dura Sealant System [EU instructions for use]; LCN 80-2005-152 Rev B.
5 Baxter, TISSEEL Knowledge in a Box.

Licensed Indications

PLEASE INSERT YOUR COUNTRY LICENSE INDICATIONS.

The efficacy in fully heparinized patients has been proven.

TISSEEL is not indicated for heavy arterial bleeding and should not be injected intravenously or used on patients who have a known sensitivity to aprotinin.

For detailed information on preparation and use of TISSEEL, see Appendix C: TISSEEL Product Details.

Studied Clinical Value of TISSEEL

Clinical studies demonstrating efficacy and safety of TISSEEL have been performed in a multitude of treatment modalities and surgical procedures and at different anatomical sites under different applications techniques, including but not limited to endoscopic/laparoscopic treatment, vascular surgery, gastrointestinal anastomoses, neurosurgery, general surgery, and pediatric patients.

A list of studies referenced in this document is provided in the table on the next page by surgical specialty.

Table 1: Summary Table of Clinical, Humanistic, and Economic Outcomes by Surgical Specialty

Specialty	Outcomes	Value Message	References
Cardiac/Cardiovascular Surgery	Clinical	TISSEEL shows a significantly higher rate of successful hemostasis and a shorter time to hemostasis, compared to other hemostatic methods	Rousou, 1989 Saha, 2011 & 2012
		TISSEEL use results in significant reductions in healthcare resource utilization, including fewer blood transfusions and shorter operating time	Kieser, 1995 Martinelli, 1995
Neuro/Spine Surgery	Clinical	TISSEEL use results in significant reductions in healthcare resource utilization, including fewer blood transfusions and shorter operating time	White, 2009
	Clinical/ Humanistic	TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity	Kassam, 2003 Seiler & Mariani, 2000 White, 2009 Yeom, 2008
	Economic	TISSEEL reduces cost of surgical and post-surgical care	Kassam, 2003
General (Hernia, Bariatric)	Clinical	TISSEEL use results in significant reductions in healthcare resource utilization, including fewer blood transfusions and shorter operating time	Lobato, 2001 Negro, 2011 Olmi, 2007
	Clinical	TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity	Benizri, 2006 Campanelli, 2012 Ceccarelli, 2008 Canonico, 1999 Fortelny, 2008 & 2012 Hidalgo, 2005 Kaul, 2012 Lau, 2005 Lobato, 2001 Lovisetto, 2007 Negro, 2011 Olmi 2007 Romeo, 1986 Schwab, 2006 Silecchia, 2008 Testini, 2010 Topart, 2005
	Economic	TISSEEL reduces cost of surgical and post-surgical care	Canonico, 1999 Lobato, 2001 Lobato, 2010
GYN/Myomectomy	Clinical	TISSEEL shows a significantly higher rate of successful hemostasis and a shorter time to hemostasis, compared to other hemostatic methods	Angioli, 2012
		TISSEEL use results in significant reductions in healthcare resource utilization, including fewer blood transfusions and shorter operating time	Angioli, 2012
ENT (Parotidectomy, Thyroidectomy)	Clinical/ Humanistic	TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity	Maharaj, 2008 Uwiera, 2005
Surgery in Cancer	Clinical/ Humanistic	TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity	Fabrizio, 1995 Gilly, 1998 Jain, 2004
Pediatric Surgery	Clinical	TISSEEL shows a significantly higher rate of successful hemostasis and a shorter time to hemostasis, compared to other hemostatic methods	Becker & Willital, 1994 Huth, 1983
	Clinical/ Humanistic	TISSEEL reduces post-operative complications; it has proven to decrease post-operative pain, reduce fluid leakage and drainage volume, and prevent seroma formations. This contributes to faster patient recovery, shorter hospital stays, improved quality of life, and quicker return to normal activities and productivity	Becker & Willital, 1994 Gopal, 2008 Sojo, 2004 Upadhyaya, 2007

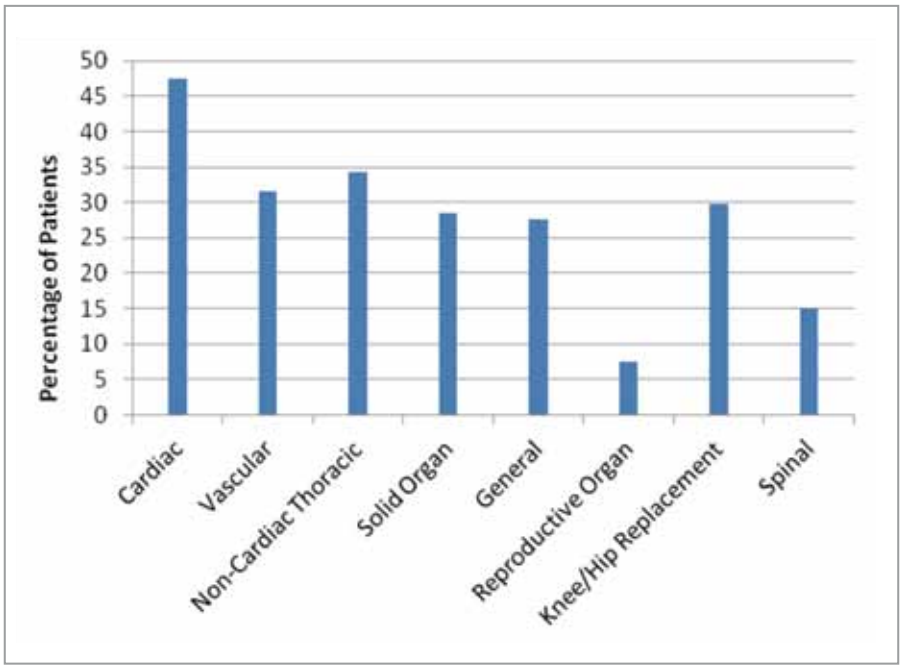
Intraoperative Surgical Challenges & Consequences

Hemostasis

Achieving and maintaining hemostasis during and after surgery is a critical requirement to the health and safety of the patient. Failure to maintain hemostasis can result in excessive bleeding, which complicates surgery and is associated with increased morbidity and mortality (Levi, 1999). Several factors contribute to hemorrhage during surgery, including the use of complex suturing, heparin, hypothermia, and cardiopulmonary bypass.

Intraoperative bleeding leads to increased operating room time, blood product transfusions, and pulmonary hypertension, all of which have significant resource costs. In a recent retrospective analysis of more than 1.6 million surgeries performed in the US, Stokes et al. reported a 29.9% average rate of bleeding-related complications among multiple surgical types (Stokes, 2011). Figure 1 displays the proportion of patients who developed a bleeding-related complication by surgery type. Patients within all surgical categories (cardiac, vascular, non-cardiac thoracic, solid organ, general, knee/hip replacement, reproductive organ, and spinal surgery) also spent more time in intensive care (ICU) with higher total hospital costs.

Figure 1: Incidence of bleeding complications by surgical type (Stokes, 2011)



Blood Transfusions

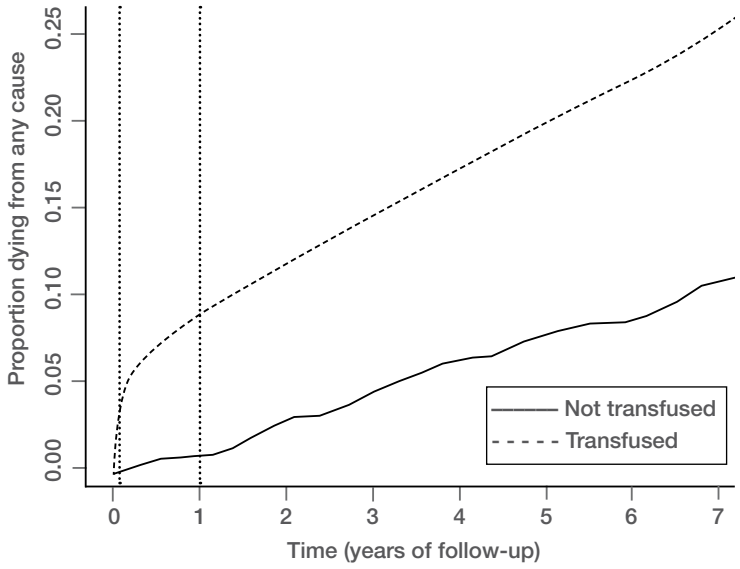
Significant blood loss frequently requires blood transfusions – usually allogeneic[6] blood transfusions (ABT). The risks of ABTs include but are not limited to:

- significantly higher risk of death (Murphy, 2007; Aronson, 2008; Kim, 2007);
- immunosuppression and bacterial infections (Goodnough, 1999; Blumberg & Heal, 1996; Hill, 2003; Chelemer, 2002);
- complications associated with contamination (Goodnough, 2005; Williamson, 1999);
- complications associated with human error (incorrect administration) [Goodnough, 2005; Williamson, 1999]; and
- slower post-operative functional recovery, especially in cardiac patients (Koch, 2006).

6 Blood from donors.

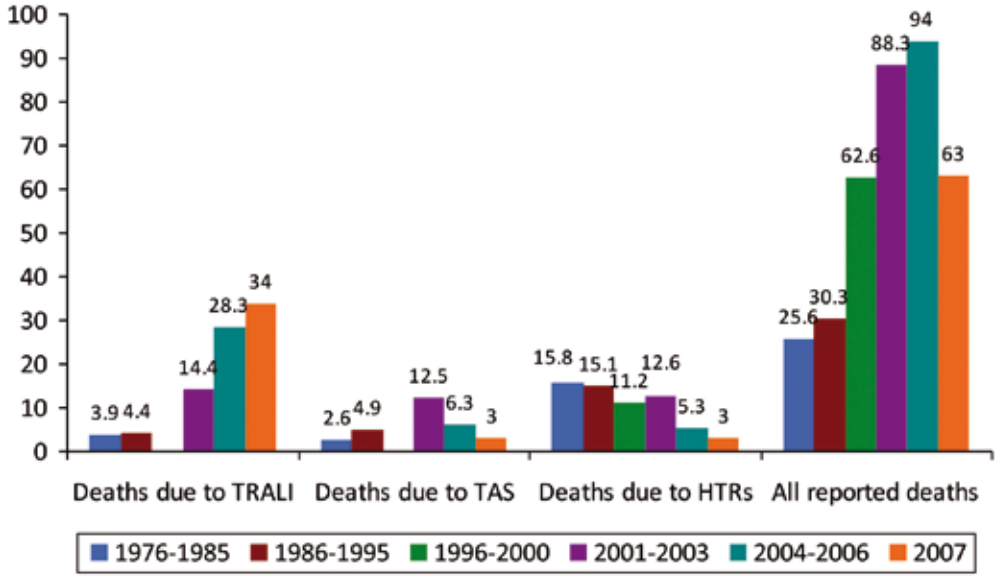
The figure below shows that up to 7 years post-surgery, patients receiving ABT have approximately double the risk of death, compared to patients who do not receive ABT.

Figure 2: Comparison of all-cause mortality with or without post-surgical transfusion (Murphy, 2007)



Attempts to reduce the risk of transfusion-transmitted viruses have been successful in the last few decades; however, transfusion-related acute lung injury (TRALI), hemolytic transfusion reactions (HTRs), and transfusion-associated sepsis (TAS) remain as causes of ABT-related deaths (Vamvakas & Blajchman, 2009).

Figure 3: Leading causes of allogeneic blood transfusion-related deaths (Vamvakas & Blajchman, 2009)



The economic consequences of blood transfusion are significant. A European analysis reported that the cost of a unit of blood transfused in a public hospital ranged from €294.83 and €339.83, and in private facilities could reach €413.93 (Kanavos, 2006). In Canada, the aggregate mean societal unit cost of red blood cells (RBCs) transfused on an inpatient basis in 2002 was US$264.81 (95% CI: $256.29-$275.65) [Amin, 2004]. A UK study estimated the costs for an adult transfusion for RBCs at £635, for fresh frozen plasma £378, for platelets £347, and cryoprecipitate of £834 (Varney & Guest, 2003). A US survey of blood bank and transfusion service directors found the mean reported acquisition cost for one unit of RBCs to be $211 (SD=38), with a mean patient charge of $344 (SD=135) [Toner, 2011].

Still, the cost of blood only accounts for part of the full cost of a transfusion. Approximately half of all transfusion costs can be attributed to non-blood related costs, including extended hospital and critical care stays and transfusion-related complications (Varney & Guest, 2003; Corwin, 2004). A study in the US found that bacterial infections following hip fracture surgery in which allogeneic blood was given increased hospitalization costs by $14,000 (Carson, 1999). Another study comparing costs between surgical patient groups who did and did not receive transfusions found charges to be $8,476 higher for the transfused cohort (p<0.0001) [Patel, 2008]. This study included patients from a range of surgical interventions.

More recently, Shander et al. adjusted per unit costs of transfused RBCs from four systematic studies to 2008 costs, and found estimated costs of transfusions to range from $332 to $717 per unit (Shander, 2010). A model accounting for acquisition costs, process steps, and direct and indirect overhead costs was designed to calculate a more accurate total cost per unit of transfused RBCs. Applying the model to two US and two European hospitals, per-RBC-unit costs ranged from $522 to $1183 ($US2008), amounts that were 3.2 to 4.8 times higher than blood acquisition costs. Abraham and Sun evaluated six western European studies on transfusion costs, including the Shander et al. study described above (Abraham & Sun, 2012). They found that the 2011 weighted mean cost of transfusing two units of RBCs to be €878 ($1225), ranging from €672 to €973.

In the 2011 study by Stokes et al. quantifying hospital costs associated with bleeding-related complications and transfusions in the US across eight surgical categories, the incremental ICU and total hospital length of stay associated with a complication or transfusion was 2.8 days (3.3 vs. 0.5 days) and 6 days (10.4 vs. 4.4 days), respectively (Stokes, 2011). For each surgery type, patients with bleeding complications/transfusion had longer hospital stays and higher costs compared to their counterparts with no surgical bleeding complications/transfusion. The incremental cost per hospitalization with bleeding complication/transfusion was $17,279 for spinal surgery, $15,123 for vascular surgery, $13,210 for solid organ, $13,473 for non-cardiac thoracic, $10,279 for cardiac, $4,354 for general, $3,005 for knee/hip, and $2,805 for reproductive organ surgery.

Increased awareness of the numerous complications associated with blood transfusion has resulted in a call for blood conservation techniques which may help minimize morbidity and mortality of surgical procedures. Use of autologous (self-donated) blood donated by the patient prior to surgical intervention may reduce patient risk, but remains associated with consequences such as bacteremia, donor reactions to own blood, iatrogenic anemia, administration errors, and volume overload (Wood & Yomotovian, 2007). Moreover, previous estimates indicate that autologous donation is approximately 60% more expensive than allogeneic blood (Tretiak, 1996). Due to the lack of convincing benefits associated with autologous blood transfusions, the procedure is not considered a cost-effective procedure (van Hulst, 2004).

TISSEEL's Value in Blood Management

Achieving and Maintaining Hemostasis

TISSEEL has demonstrated efficacy in achieving timely hemostasis. One of the first studies in cardiac surgery patients undergoing resternotomy or reoperation demonstrated TISSEEL's superiority in achieving hemostasis in less than 5 minutes, compared with conventional treatment, as shown in the table below (Rousou, 1989).

Table 2: Hemostasis with TISSEEL and conventional treatment in cardiac surgery (Rousou, 1989)

	TISSEEL	Control
Number of patients	164	169
Bleeds	214	97
Hemostasis achieved in <5 minutes	92.6%* (198/214)	12.4% (12/97)

* Statistical significance comparing successful hemostasis, p<0.001.

More recently, TISSEEL's performance in suture-hole bleeding at **vascular anastomoses** was compared to manual compression in Phase II and Phase III studies (Saha, 2011; Saha, 2012). In phase II, Saha et al. reported superiority in TISSEEL to achieve hemostasis within 4 minutes, compared to sutures (62.5% vs. 34.8%, respectively), for a relative improvement of 79.6% (Saha, 2011).

Similarly, in Phase III, hemostasis within 4 minutes was achieved more often with TISSEEL than with the control. The results are shown in the table below (Saha, 2012).

Table 3: Hemostasis with TISSEEL vs. manual compression (Saha, 2012)

Study Group	Hemostasis achieved in 4 mins N (%)	Additional treatment required to achieve hemostasis N (%)	Intraoperative rebleeding after primary hemostasis N (%)	Hemostasis achieved at 4 mins & maintained until surgical closure N (%)
TISSEEL	47 (67.1)	13 (18.6)	4 (5.7)	44 (62.9)
Control	22 (31.4)	28 (40.0)	1 (1.4)	22 (31.4)

Timely hemostasis has also been demonstrated in laparoscopic **myomectomy.** Angioli et al. reported that mean time to hemostasis was 195.5 seconds with TISSEEL compared to 361.8 seconds with sutures ($p<0.0005$), and that the mean estimated blood loss was 111.3 mL with TISSEEL compared to 230 mL with sutures ($p<0.05$) [Angioli, 2012].

Table 4: Hemostasis and blood loss with TISSEEL vs. sutures in myomectomy (Angioli, 2012)

	TISSEEL (mean ± SD)	Sutures (mean ± SD)	Significance
Time to hemostasis (seconds)	195.5±40.9	361.8±116.0	$p<0.0005$
Estimated intraoperative blood loss (mL)	111.3±77.3	230.0±75.6	$p<0.05$

Reducing Blood Transfusions and Blood Product Usage

As previously mentioned, inability to achieve or maintain hemostasis can lead to multiple consequences, including blood transfusion, increased operating time, increased risk of post-operative complications and infections, increased drainage volume, and increased duration of hospital and ICU stays. Multiple studies have demonstrated a reduction in negative outcomes and resulting healthcare resource utilization with TISSEEL use during surgeries, **specifically cardiovascular surgery, hernia repair, and neurosurgery.**

Minimizing blood loss can result in fewer blood transfusions and reduced amounts of blood products. In **cardiac surgery,** two studies have reported less blood product use with TISSEEL or TISSEEL + aprotinin. Martinelli et al. reported less packed red cells were collected and processed according to a cell-saver protocol in heart transplant patients receiving TISSEEL + aprotinin (mean±SD = 55±25 mL vs. 250±70 mL in the control; $p<0.001$) [Martinelli, 1995]. Kieser et al. found **open heart surgery** patients had significantly less blood transfusion units with TISSEEL compared to the comparator group ($p<0.01$) [Kieser, 1995]. Similar results were found in incisional **hernia repair**; more sutures patients required blood transfusion due to hematoma, compared to TISSEEL patients (Lobato, 2001). And in **cranial procedures,** White et al. reported that 2 (20%) of 10 patients in the non-TISSEEL group required post-operative transfusion, while none of the TISSEEL cohort did (White, 2009).

Table 5: Differences in blood product use and transfusions

Author, Year	Surgery	Outcome Measure	TISSEEL Results	Comparator Results	Significance
Martinelli, 1995	Heart transplant	RBCs collected and processed	55±25 mL	250±70 mL	p<0.001
Kieser, 1995	Open heart surgery	Blood transfusion units	1st TISSEEL group: 10.3U 2nd TISSEEL group: 13.2U	23.7U	p<0.001 p<0.01
Lobato, 2001	Incisional hernia repair	Transfusion*	0%	13.3%	p<0.001
White, 2009	Cranial procedures	Transfusion*	0%	20%	-

* Post-operative transfusions

Fluid Leakage

Inadequate sealing of anastomeses or suture lines can result in intraoperative (as well as post-operative) challenges including cerebrospinal fluid (CSF) leaks, anastomosis leaks, and prophylactic drainage.

CSF leakage is an abnormal drainage of cerebrospinal fluid from the subarachnoid space in the brain. In most circumstances, the fluid is observed leaking from the ears, nose, or an open wound (Kaplan, 2000). CSF leaks pose a risk of significant morbidity with the potential for meningitis and migraine headaches, as well as development of pseudomeningocele. Management practices often consist of insertion of a spinal fluid drain, as well as administration of prophylactic or therapeutic antibiotics (Elgamal, 2008). However, in cases of persistent CSF leakage, surgical re-exploration may be necessary.

Treatment of CSF leaks may increase cost of care by as much as 141% (Grotenhuis, 2005). A summary of the cost in Euros to treat CSF leaks is shown in the figure below.

Figure 4: Cost of treating CSF leaks compared to no leaks (Grotenhuis, 2005)

Leaking anastomosis is a significant concern during intestinal surgery (Kayahara, 1995). A leaking anastomosis occurs in approximately 3% of intestinal procedures, and is associated with significant morbidity or mortality (Hyman, 2007). The cost consequences are primarily attributed to hospital and intensive care stays for re-surgery. A study in Australia reported that patients with a leaking anastomosis were hospitalized for an average of 32 days (range 13 – 67), with 3.2 days (range 0 – 14) spent in ICU (Platell, 2005). The additional costs of an anastomotic leak were estimated to be between $35,000 and $40,000.

Prophylactic drains are often inserted during surgical procedures to remove intraperitoneal collections such as ascites, blood, bile, and chyle, and to possibly decrease seroma formation, wound dehiscence, and infections. Prophylactic drains require a high level of maintenance, can cause discomfort, interfere with mobility, and serve as potential routes for infection when drainage is prolonged. Early drain removal can reduce multiple negative outcomes.

Therefore, strategies that can be used to prevent post-operative fluid accumulation may decrease morbidity, decrease costs, and increase patients' quality of life by reducing drain duration or eliminating the use of the drains altogether.

TISSEEL's Value as a Sealant

Fluid leakage may be reduced with TISSEEL use. Studies report **less risk of CSF leakage, less risk of anastomotic leakage, and less prophylactic drainage volume.** Two neurosurgical studies have reported benefits of TISSEEL to **reduce risk of CSF leakage.** Seiler and Mariani reported on their 10-year experience using TISSEEL with 376 patients undergoing sellar reconstruction after transsphenoidal surgery between 1989 and 1999 in Switzerland (Seiler & Mariani, 2000). They reported two patients (0.5%) had persistent CSF leakage when TISSEEL was used, compared to a US reported national rate of 1.5% (Ciric, 1997). Similarly, in patients undergoing anterior cranial base, infratemporal, or retromastoid surgical procedures for intracranial pathological lesions, Kassam et al. reported that the incidence of CSF leaks without TISSEEL varied from 4-16%, depending on surgical approach, with an overall incidence rate of 5.5% (10 of 181 cases) [Kassam, 2003]. However, with TISSEEL use, they reported no CSF leaks (p=0.067).

In digestive surgery, two studies have reported a **reduction in anastomosis leakage** with TISSEEL use. In a laparoscopic Roux-en-Y gastric bypass (LRYGBP) study, Silecchia et al. reported one anastomotic leak with TISSEEL, compared to three leaks with no TISSEEL, and zero anastomotic bleeding with TISSEEL, compared to two bleeding events with no TISSEEL (Silecchia, 2008). Similarly, Romeo et al. evaluated the role of TISSEEL to prevent anastomotic dehiscence (i.e., rupture) in **digestive surgery** and reported 25% minor leaks in 32 **colorectal and esophagojejunal anastomoses** when no sealant was used, compared to 2.4% leaks (1 patient out of 42) when TISSEEL was used to seal the suture/staple line (Romeo, 1986).

Finally, TISSEEL has also been reported to **decrease drainage volume** (post-operatively) in procedures such as **cervical fusion, scalp closure, parotidectomy, and thyroidectomy.** An analysis of anterior cervical fusion compared TISEEEL to control in decreasing post-operative drain output and reported significantly less drainage with TISSEEL use (47 mL vs. 98 mL, respectively, p<0.0001) [Yeom, 2008]. Time for the drainage to decrease to <20 mL per shift was also significantly reduced with TISSEEL use (17 hours vs. 24 hours, respectively, p=0.0054). Similarly, White et al. reported that drainage volume in the first 8 hours following scalp closure was less with TISSEEL (172 mL compared to 246 mL in the non-TISSEEL group, p<0.02), as was total drainage (301 mL with TISSEEL compared to 441 mL in the non-TISSEEL group, p<0.01) [White, 2009].

In Canada, Maharaj et al. assessed TISSEEL use in **parotidectomy** and also reported a significant difference in total wound drainage, with TISSEEL patients yielding 41.3 mL vs. the non-TISSEEL mean volume of 65.3 mL (p<0.02) [Maharaj, 2006]. Similarly, Uwiera et al. reported a significant reduction in drainage (nearly 50%) in the first 8-hour post-operative period, and a 43% reduction in drainage in the total 64-hour observation period with TISSEEL use in **thyroidectomy procedures** (Uwiera, 2005).

Table 6: Differences in drainage output

Author, Year	Study Population	TISSEEL Drainage Volume	Comparator	Comparator Drainage Volume	Significance
Yeom, 2008	Multilevel anterior cervical fusion (N=30 per cohort)	Total drain output: 47 mL	No TISSEEL	Total drain output: 98 mL	p<0.0001
White, 2009	Calvarial remodelling for sagittal synostosis (N=6 TISSEEL vs. N=10 control)	Total drain output: 301 mL	No TISSEEL	Total drain output: 441 mL	p<0.01
Maharaj, 2006	Parotidectomy (N=30 per cohort)	41.3 mL	No TISSEEL	65.3 mL	p<0.02
Uwiera, 2005	Thyroidectomy (N=26 TISSEEL vs. N=30 control)	First 8 hours: 30.9 mL	No TISSEEL	First 8 hours: 55.1 mL	p<0.001

TISSEEL's Value in Reducing Operating Room Times

Use of TISSEEL can also lead to reduced operating room times. Three studies in inguinal **hernia repair** and one study in **myomectomy** have reported decreased OR times of 5 to 17 minutes. Results from a study on plug and patch hernia repair patients with and without TISSEEL demonstrated a 10-minute reduction with TISSEEL use in unilateral hernia repair (p=0.0017), and a 16-minute reduction with TISSEEL use in bilateral hernia repair (p=0.0008) [Benizri, 2006]. Olmi et al. reported on differences in four mesh fixation methods following laparoscopic transabdominal preperitoneal (TAPP) inguinal hernioplasty and demonstrated that among unilateral hernia cases, TISSEEL was associated with shorter operating times (30 minutes compared to 35, 36, and 38 minutes in the other three fixation method groups, p<0.05) [Olmi, 2007]. Similarly, Negro et al. found average operation time to be 55.6 minutes in TISSEEL patients vs. 61.2 minutes with sutures (p<0.001) [Negro, 2011].

Finally, Angioli et al. reported on TISSEEL versus sutures in laparoscopic myomectomy and reported that TISSEEL patients had a mean operating time of 47.7 minutes, compared to 62.1 minutes in sutured patients (p<0.05) [Angioli, 2012].

Table 7: Differences in operating times between TISSEEL and comparators

Author, Year	Study Population	TISSEEL OR Time in minutes	Comparator (s)	Comparator OR Time in minutes	Significance
Benizri, 2006	Open primary hernia repairs with plug and patch mesh (N=57 per cohort)	Uni: 44±9 Bi: 82±10	Non-absorbable sutures	Uni: 54±11 Bi: 98±10	Uni: p=0.0017 Bi: p=0.008
Olmi, 2007	TAPP inguinal hernia (N=150 per cohort)	Uni: 30 Bi: 50	Staple product 1 Staple product 2 Staple product 3	Uni: 35 Bi: 50 Uni: 36 Bi: 52 Uni: 38 Bi: 55	Uni: p<0.05 Uni & Bi: p<0.05 Uni & Bi: p<0.05
Negro, 2011	Inguinal hernia repair (N=349 TISSEEL vs. N=171 control)	55.6±14.6	Sutures	61.2±14.5	p<0.001
Angioli, 2012	Laparoscopic myomectomy (N=15 per cohort)	47.7±15.4	No TISSEEL	62.1±21.1	p<0.05

Uni=unilateral; Bi=bilateral; OR = operating room; TAPP = laparoscopic transabdominal preperitoneal inguinal hernioplasty; vs = versus

Post-operative Challenges & Consequences

Pain

While post-operative pain is often an expected outcome of surgery, effective relief of pain is paramount, both for humanitarian reasons and physiological benefit. Not only does effective pain relief mean a smoother post-operative course with earlier hospital discharges, but it may also reduce the onset of chronic pain syndromes. Several factors affect patients' perception of post-operative pain, including the type of intervention, complications, age, individual tolerance, and pain scores (which are predictive of recovery time regardless of surgical intervention) [Pavlin, 2002]. In most circumstances, post-surgical pain is associated with use of staples or sutures, and many studies have assessed consequences of pain on quality of life, narcotic use, and ability to return to work or school.

TISSEEL's Value in Reducing Post-operative Pain

Reducing Pain and Improving Quality of Life

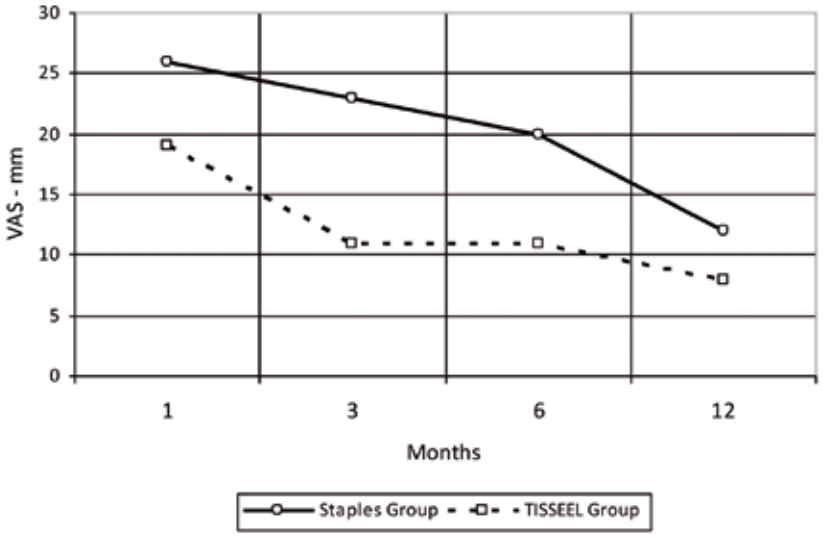
TISSEEL has demonstrated value in reducing post-operative pain and discomfort, thereby reducing analgesic use and returning the patient to normal activity and productivity quicker. Most studies providing evidence of TISSEEL's value in these humanistic outcomes have been conducted in **hernia repair.**

Several studies on post-operative pain have been conducted in transabdominal preperitoneal (TAPP) inguinal hernioplasty. In laparoscopic TAPP inguinal hernioplasty, Olmi et al. compared pain scores one month after surgery with one of four mesh fixation methods (Olmi, 2007). Results demonstrated that resumption to work was quicker among TISSEEL

patients (5 days compared to 7 and 9 days in the other fixation groups, p<0.05), and that post-operatively, TISSEEL patients reported less pain. Ceccarelli et al. reported similar results as well; their study demonstrated that post-operative pain at the 10 mm trocar site was greater in the staples group than with TISSEEL use (Ceccarelli, 2008). They also reported that four (5.9%) staples patients reported significant pain scores, compared to no (0%) TISSEEL patients (p<0.05).

Lovisetto et al. found similar results: patients with TISSEEL reported less pain and less use of analgesics, compared to patients with staples (Lovisetto, 2007). (See Figure 5.) In addition, TISSEEL patients returned to work and normal social life one month sooner.

Figure 5: Mean pain scores at 1, 3, 6, and 12 months post hernia repair* (Lovisetto, 2007)



VAS: visual analog scale, representing severity of pain (0=no pain, 100=maximum pain). P<0.001 at months 1, 3, and 6.

Less pain with TISSEEL has also been reported in total extraperitoneal (TEP) laparoscopic repair of unilateral or bilateral groin hernias, in open Lichtenstein repair of inguinal hernia, and in plug and mesh procedures.

Three studies have assessed acute and chronic pain and/or analgesic use in TEP repair. Topart et al. reported that patients receiving staples during TEP repair complained of pain in the groin area more than 3 months after surgery, while only three (4.5%) of the patients in the TISSEEL group complained of groin area pain (p=0.037) [Topart, 2005]. Schwab et al. also compared outcomes associated with TISSEEL vs. staples and reported that pain was significantly more likely in the staples group: 18 (20.7%) staples patients vs. four (4.7%) TISSEEL patients were documented with chronic pain (p=0.002) [Schwab, 2006]. In addition, 10 of the 18 staples cases and none of the TISSEEL cases required local infiltrations of anesthetics. Lau also reported less use of analgesics with TISSEEL compared to staples (4.5 tablets vs. 7 tablets, respectively, p=0.03) following endoscopic extraperitoneal bilateral inguinal hernia repair (Lau, 2005).

A recent meta-analysis assessing studies on TEP and TAPP procedures with TISSEEL versus staple/tack fixation summarized the studies as follows: chronic pain at 3 months was significantly higher with staples compared to TISSEEL (OR 3.25, 95% CI 1.62-6.49) [Kaul, 2012].

Quality of life is also reported to improve with TISSEEL use in TAPP hernia repair. Fortelny et al. reported marked improvement in six of eight quality of life dimensions in the SF-36 among patients receiving TISSEEL in laparoscopic TAPP repair (Fortelny, 2008). (See table below.)

Table 8: Differences in mean SF-36 scores by dimension (Fortelny, 2008)

SF36 Measures	Mean	SD	Median	Minimum	Maximum	Range	P Value*
Physical function	14.1	20.0	5.0	-10.0	55.0	65.0	0.0352
Role physical	36.4	39.3	25.0	0.0	100.0	100.0	0.0313
Bodily pain	39.5	19.4	38.0	16.0	69.0	53.0	0.0010
General health	8.9	10.6	5.0	0.0	33.0	33.0	0.0078
Vitality	3.6	21.5	0.0	-30.0	50.0	80.0	0.7969
Social function	18.2	22.6	12.5	0.0	62.5	62.5	0.0313
Role emotional	21.2	45.4	0.0	-33.3	100.0	133.3	0.2500
Mental health	6.2	12.6	4.0	-8.0	32.0	40.0	0.2109
Physical summary	10.8	6.4	8.6	2.4	19.6	17.2	0.0010
Mental summary	2.6	8.7	-0.4	-8.1	20.1	28.2	0.5771

*P<0.05 indicates statistically significant improvement in measures 1 year post-operatively compared to pre-operatively

In a later publication, Fortelny et al. reported that physical health, as measured by the SF-36, was improved significantly with TISSEEL use in 3 months, while patients receiving staples reported significant increases after 1 year (Fortelny, 2012). Mental health was also improved after 3 months in TISSEEL patients, while mental health did not improve during the observation period in patients with staples.

In Lichtenstein repair of inguinal hernia (an open procedure, versus the laparoscopic TEP and TAPP repairs), short-term and long-term pain is reported to be decreased in three studies assessing TISSEEL. Negro et al. reported that patients receiving TISSEEL reported less pain in the short-term: mean pain score in the TISSEEL group was 2.5, compared to the suture group mean score of 3.2 (p<0.001) [Negro, 2011]. At month 1, less patients in the TISSEEL group reported pain, numbness and/or discomfort, and reported less intense pain if present (mean VAS score of 0.6 in TISSEEL compared to 1.2 in sutures groups, p=0.001). Hidalgo et al. reported that Lichtenstein bilateral hernia repair patients receiving TISSEEL experienced less short- and long-term pain, compared to sutures (Hidalgo, 2005). In their study, average pain scores and use of analgesics were significantly lower with TISSEEL. By 30 days, 80% of hernias treated with TISSEEL had no pain, 18% had mild, and 1.8% had moderate pain. At 1 year, all TISSEEL-treated hernias were pain-free. In comparison, by 30 days, 32% of hernias treated with sutures were pain-free, while 47.2% were causing mild pain, and 25.4% were causing moderate pain. Similarly, Campanelli et al. assessed pain and discomfort following Lichtenstein repair for primary unilateral inguinal hernia (Campanelli, 2012). TISSEEL patients were less likely to report at least one disabling complication at 12 months (8.1% compared to 14.8%, respectively, p=0.0344), reported less pain at 1 and 6 months (p=0.0132; p=0.0052), and were less likely to continue use of analgesics to treat pain (65.2% vs. 79.7%, respectively, p<0.001).

In plug and mesh procedures for inguinal hernias, two studies have demonstrated TISSEEL's superiority in diminishing pain. Benizri et al. reported that at 12 months post-surgery, two of 57 patients with TISSEEL suffered chronic inguinal pain, with one (1.3%) describing pain as mild and the other as moderate (1.3%) [Benizri, 2006]. Among the 57 patients with sutures, 13 patients reported pain, and of those, eight (15.8%) were mild, three (5.3%) were moderate, and two (3.5%) were severe. The incidence of chronic pain was therefore significantly higher in the sutures group (22.8% vs. 3.5%, p=0.042). Similarly, Testini et al. assessed short-term (or acute) and chronic pain comparing three fixation methods (Testini, 2010). Long-term follow up revealed TISSEEL was associated with less sensation and chronic pain as shown in the table below.

Table 9: Number (%) of hernias with long-term outcomes by fixation method (Testini, 2010)

Complication	Sutures (n=59)	TISSEEL (n=52)	N-butyl-2-cyanoacrylate (n=56)
Chronic pain	2 (3.4%)	0	0
Sensation of extraneous body	5 (8.7%)	0	1 (1.8%)
Total	7 (11.9%)	0	1 (1.8%)

Suture vs. TISSEEL, p=0.01; suture vs. N-butyl-2-cyanoacrylate, p=0.03, TISSEEL vs. N-butyl-2-cyanoacrylate, p=0.16

Seroma Formation

Post-surgical seroma formation, a subcutaneous collection of serous fluid, is a common complication in many surgeries. For example, it is the most common complication of mastectomy (Stehbens, 2003) and is often reported after hernia repair (Morales-Conde, 2012). Seromas can cause pain and may interfere with surgical site healing, and often require treatment (e.g., drainage, antibiotic therapy, surgery).

TISSEEL's Value in Preventing Seroma Formation

Seroma formation and other post-operative complications have been reported to decrease in frequency with TISSEEL use in **parotidectomy and breast surgeries.** Maharaj et al. reported a reduction in seroma formation with TISSEEL use following parotidectomy, from 22.7% to 3.6% ($p<0.05$) [Maharaj, 2006]. In another study, patients with newly diagnosed breast cancer and undergoing breast surgery were randomized to prophylaxis drain, no drain, or no drain plus TISSEEL (Jain, 2004). Results demonstrated that the rate of seroma formation was highest in mastectomy patients without a drain and without fibrin sealant ($p=0.048$).[7]

Wound Dehiscence

Wound dehiscence, a partial or complete separation of a surgical suture, is a serious post-operative complication occurring in 1-3% of surgery patients overall (Hahler, 2006). Additional healthcare resources are required for dehiscence treatment and hospital lengths of stay may increase. If a dehisced wound leads to evisceration (internal organ protrusion), surgery is often required.

TISSEEL'S Value in Preventing Wound Dehiscence

Wound dehiscence and inflammation may be reduced with TISSEEL use. The efficacy of TISSEEL was investigated in a randomized controlled study to explore differences in infectious complication rates following prolonged reconstructive procedures after **ablative cancer surgery** (Fabrizio, 1995). Results showed that the TISSEEL group experienced less wound dehiscence (4.8% with TISSEEL vs. 20.5% without TISSEEL) and inflammation (1.9% with TISSEEL vs. 14.7% without TISSEEL). Furthermore, the onset of scar hypertrophy was reduced in the TISSEEL-treated group (11.7%) vs. control (34.2%).

Other Clinical Benefits

Other clinical benefits have been demonstrated with TISSEEL use. In inguinal **hernia repair,** Canonico et al. demonstrated TISSEEL's efficacy to prevent coagulative complications among patients with coagulation disorders (Canonico, 1999). They reported that post-operative hemorrhagic complications were reduced from 24% in the control group to 4% with TISSEEL. Lobato et al. reported less risk for cellulitis and hematoma formation following incisional hernia repair (Lobato, 2001). They also reported 20% of the control group experienced cellulitis, compared to 3.3% of TISSEEL patients ($p<0.01$), and 20% of the control group developed hematoma, compared to 6.6% of TISSEEL patients ($p<0.01$).

7 The incremental value of TISSEEL vs. drain is difficult to ascertain in this study.

Table 10: Differences in post-surgical complications

Author, Year	Study Population	Outcome Measure	TISSEEL Results	Comparator Results	Significance
Maharaj, 2006	Parotidectomy	Seroma formation	3.6%	22.7%	p<0.05
Jain, 2004*	Mastectomy	Seroma formation	42.1%	83.3%	p=0.048
Fabrizio, 1995	Reconstructive procedures after ablative cancer surgery	Wound dehiscence Inflammation Scar hypertrophy	4.8% 1.9% 11.7%	20.5% 14.7% 34.2%	sig sig sig
Canonico, 1999	Inguinal hernia repair among pts with coagulation disorders	Hemorrhagic complications	4%	24%	p=0.049
Lobato, 2001	Incisional hernia repair	Cellulitis Hematoma	3.3% 6.6%	20% 20%	p<0.01 p<0.01

*TISSEEL/no drain vs. no Tisseel/no drain

Recovery Time/Hospital Stays

As expected, most surgical complications lead to further treatment and require additional hospital days. Benizri et al. found TISSEEL patients with shorter hospital stays compared to suture patients after inguinal hernia repair (1.8±0.9 days vs. 2.4±0.7 days, p<0.0001) [Benizri, 2006]. In an analysis of patients with coagulation disorders undergoing hernia repair, Canonico et al. reported that all TISSEEL patients were discharged after 24 hours of surgery, while six patients in the control group had prolonged stays due to complications (Canonico, 1999). Also in incisional hernia repair, Lobato et al. reported the average hospital length of stay was 7.1 days with TISSEEL vs. 12.6 days without TISSEEL. The difference in duration of hospitalization was largely due to wound infection and hematomas (Lobato, 2001). In laparoscopic transabdominal preperitoneal (TAPP) inguinal hernioplasty, Olmi et al. reported that hospital length of stay was statistically significantly less for patients treated with TISSEEL compared with three other prosthesis fixation methods (1.0 day, compared to 1.1 and 1.2 days in other groups, p<0.05) [Olmi, 2007].

In cervical fusion surgery, Yeom et al. reported patients with TISSEEL had an average length of stay of 1.2 days compared to 2.1 days with no TISSEEL (p<0.0001) [Yeom, 2008].

Gilly et al. reported that TISSEEL use resulted in shorter hospital duration following lymphadenectomy, compared to no TISSEEL use (TISSEEL: 8±1.6 days vs. no TISSEEL 10.1±2.1 days, p=0.006) [Gilly, 1998]. In prolonged reconstructive procedures after ablative cancer surgery, Fabrizio et al. reported a reduction in hospital stay from 25 days in the control group to 10.5 days when TISSEEL was used, largely due to reduced post-operative infection rates (Fabrizio, 1995). Conboy and Brown reported that use of TISSEEL in parotidectomy contributes to avoidance of inpatient admission entirely and allows the procedure to be conducted on outpatients (Conboy & Brown, 2008).

Table 11: Differences in hospital length of stay

Author, Year	Study Population	TISSEEL LOS	Comparator	Comparator LOS	Significance
Benizri, 2006	Open primary hernia repairs with plug and patch mesh (N=57 per cohort)	1.8±0.9 days	Non-absorbable sutures	2.4±0.7 days	p<0.0001
Canonico, 1999	Inguinal hernia repair among pts with coagulation disorders (N=25 per cohort)	100% discharged <24 hrs	No TISSEEL	76% discharged <24 hrs	
Lobato, 2001	Incisional hernia repair	7.1 days	No TISSEEL	12.6 days	p<0.01
Olmi, 2007	TAPP inguinal hernioplasty (N=150 per cohort)	1.0 day	Protak EndoANCHOR EMS	1.1 days 1.1 days 1.2 days	p<0.05
Yeom, 2008	Cervical fusion surgery (N=30 per cohort)	1.2 days	No TISSEEL	2.1 days	p<0.0001
Gilly, 1998	Lymphadenectomy (N=50 TISSEEL vs. N=58 control)	8.0±1.6 days	No TISSEEL	10.1±2.1 days	p=0.006
Fabrizio, 1995	Reconstructive procedures after ablative cancer surgery (N=102 TISSEEL vs. N=112 control)	10.5 days	No TISSEEL	25 days	

LOS = length of stay

TISSEEL's Value in Pediatric Studies

A few pediatric studies comparing TISSEEL patients to a control group have been conducted in different surgical areas. These studies demonstrate TISSEEL's association with significantly fewer post-operative complications in pediatric surgeries.

Post-operative blood loss was compared in a pediatric cardiac surgery study (tetralogy of Fallot correction and Senning-procedure in transposition of the great arteries) between groups of children who did and did not receive TISSEEL (Huth, 1983). Blood loss with TISSEEL was significantly less at 2 hours ($p<0.01$), 6 hours ($p<0.01$), and 12 hours ($p<0.05$) after surgery compared to the control groups.

Table 12 : Post-operative bleeding with and without TISSEEL in cardiac surgery (Huth, 1983)

Surgery	Post-operative Period	TISSEEL Blood Loss* (mean ± SD)	No TISSEEL Blood Loss* (mean ± SD)	Significance
Tetralogy of Fallot		N=21	N=20	
	0-2 hours	2.2±1.4	4.2±2.3	p<0.01
	3-6 hours	1.0±0.8	1.2±0.9	p<0.05
	0-6 hours	1.4±1.0	2.2±1.4	p<0.01
	0-12 hours	1.1±0.5	1.5±0.8	p<0.05
Transposition of the great arteries		N=10	N=10	
	0-2 hours	2.4±1.2	4.5±2.2	p<0.01
	0-6 hours	1.9±1.0	2.5±1.1	p<0.01
	0-12 hours	1.5±0.7	1.8±0.8	p<0.05

*Blood loss measured in mL/hr/kg

In infants with long-gap esophageal atresia with tracheoesophageal fistula, Upadhyaya et al. found that esophageal anastomotic leaks occurred in 9.1% of patients with TISSEEL and 43% of patients without TISSEEL ($p=0.017$) [Upadhyaya, 2007]. Post-operative esophageal stricture incidence was 10% vs. 41% in TISSEEL and control patients, respectively ($p=0.028$).

Becker and Willital reported on children who underwent liver resection, partial resection of the kidney, or resection of the pancreas over a 10-year period (Becker & Willital, 1994). Laser resection of the liver was performed with and without TISSEEL application. Patients with TISSEEL had half the secretion volume on day 2 (15 vs. 30 mL) and day 3 (10 vs. 20 mL) of those without TISSEEL. Post-operative complications (e.g., bleeding, infection, urinary fistula) were significantly lower with TISSEEL than without in kidney resection patients. Similar results were found for those children undergoing pancreas resection.

Table 13: Post-operative complications with and without TISSEEL in liver, kidney, and pancreatic surgery (Becker & Willital, 1994)

Surgery	Post-operative Complications	TISSEEL	No TISSEEL
Liver resection		N=19	N=22
	Day 1 secretion	15mL	30mL
	Day 3 secretion	10mL	20mL
	Abscess	0%	27.3%
Kidney resection		N=12	N=17
	Bleeding	8.3%	23.5%
	Infection	0%	52.9%
	Urinary fistula	0%	47.1%
Pancreas resection		N=20	N=34
	Bleeding	0%	29.4%
	Infection	5.0%	35.3%
	Urinary fistula	10.0%	26.5%

P values not reported

Post-operative complications were also less common with TISSEEL in a study of surgical hypospadias repair (Gopal, 2008). A significantly lower proportion of children who received TISSEEL experienced edema (16.7% vs. 35.0%; p=0.039), urethrocutaneous fistula formation (10.0% vs. 31.7%; p=0.027), and overall post-operative complications (20.0% vs. 56.7%; p=0.003).

In a study of children receiving peritoneal dialysis catheters, half of the catheters were implanted with an application of TISSEEL to the peritoneal cuff suture (Sojo, 2004). The proportion of TISSEEL patients to develop dialysate leakage from the catheter was significantly lower in the TISSEEL group compared to the control group (11% vs. 54%; p<0.02). Of those catheters that were used within 5 days ("early-used catheters"), leakage was present in 9% of the TISSEEL group, compared to 57% of the control group (p<0.05).

Studied Economic Value of TISSEEL

To date, a limited number of studies have explored the economic consequences of using TISSEEL fibrin sealant in surgical procedures. As discussed above, most studies report resource reduction with TISSEEL: shorter hospital stays, fewer adverse events and complications, and a lower reoperation rate. These results may lead to associated savings, but this is not empirically proven. However, avoided costs with the use of TISSEEL have been specifically reported in surgical areas such as hernia repair, neurosurgery, and others.

The following section describes the economic value of TISSEEL to reduce healthcare costs. The section also discusses several budget impact models based on some of the most important surgical applications of TISSEEL. Budgetary impact enables hospital administrators to set budgets and monitor usage.

For budget impact models to be informative, they should be constructed so that they are aligned with licensed indications and are ideally based on randomized studies or combined analysis of available studies in similar indications. With respect to fibrin sealants, this is important because the different preparations available vary according to indication, composition, and handling and are not considered generics of one another (Tredtree, 2006).

The data presented here may not represent the actual cost differences in your market. Therefore, these figures cannot be used directly in your institution. Rather, these figures are provided so that you can gain insights into what the results might look like in your market. To effectively use these models, you will need to identify your own, local cost estimates. The key element to adapting a BI model for use locally is identification of any differences in treatments practices and, most importantly, the local cost data. For each BI model, we provide a table describing the costing data that need to be identified to adapt the model. The representative studies used to develop each of the models are described below.

Model Design

Cost data in model

For each of the TISSEEL budget impact model the average cost per treated case has been estimated. The average cost includes the proportion of subjects that experience adverse events (AEs) attributed to surgery and the resulting increase in costs, and those cases that did not experience AEs. Therefore, the "average cost per case" includes the costs for normal case (i.e., no AE) and cases that failed and experienced AEs or may have required additional follow-up. Therefore, the "average cost per case" generated by the model represents an average of all patients treated using a surgical procedure which includes the costs of the surgical procedure and all costs required to treat AEs.

Estimating the "average cost per case" enables you to calculate the macro level budgetary impact related to a surgical procedure. By multiplying the "average cost per case" with the number of procedures performed per center within a given year, you can obtain the budget impact. For example, if the "average cost per case" is €1,000, and there are 100 cases performed in a year, the budget impact would be €100,000.

Within the model the "average cost per case" is calculated by multiplying the outcome event frequency with cost per item or adverse event rate. This is done for the major cost items incurred during the procedure. This enables estimating the disaggregated cost which makes up the average cost per case. The individual items are then summarized to provide

the “average cost per case.” The budget impact models are limited by the data reported in the clinical trials used to develop these models.

The costs are reported in aggregated and disaggregated format. This enables comparison of difference in cost elements either with or without TISSEEL.

The ‘total budgetary impact’ can be derived from the average cost per case multiplied by the number of cases per year. By multiplying the average cost per case and the total case, this gives budget holders an estimate of the total costs of treatment that also includes the adverse events costs.

Avoidable Outcomes in Budget Impact Models

The outcomes used to derive the costs for the three BI models were taken directly from the published manuscripts. A summary of the outcomes on which the costs were based are presented in the appropriate section for each of the models.

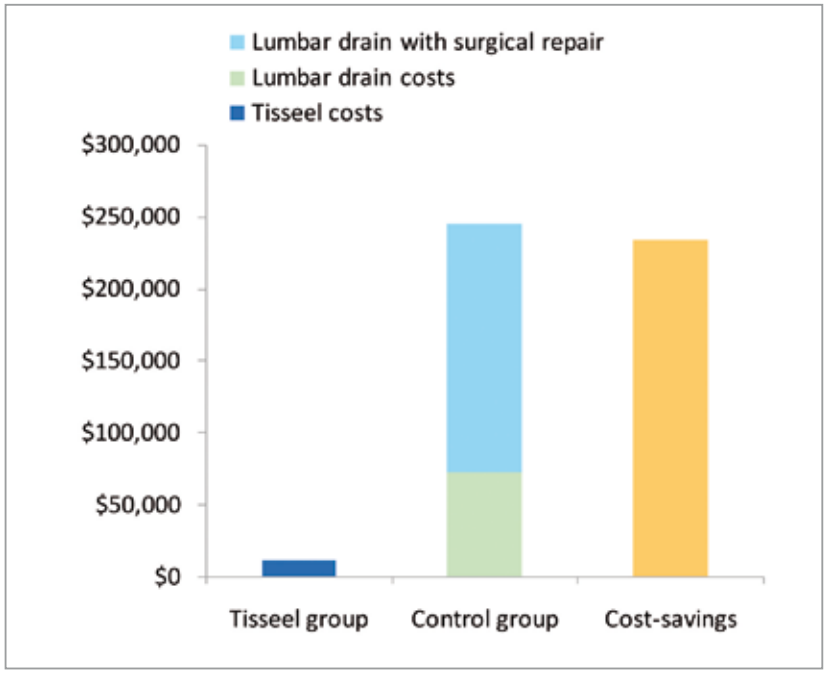
No adjustments were made for quality of life attributed to surgical failure rates or adverse events reported in the manuscripts. This would have required a cost utility analysis which was beyond the scope for this exercise to estimate budgetary impact. However, if we had included some element around quality of life, TISSEEL would have shown an even bigger advantage relative to the comparators used in the trials.

Budget Impact - Neurosurgery and CSF Leak

Cerebrospinal leaks often occur following neurosurgical interventions. CSF leaks are associated with high morbidity and costs, therefore minimizing these events can have significant cost savings. To understand the impact of CSF leaks on resources, we have developed a budget impact model based on the study reported by Kassam et al. (Kassam, 2003). The study was a retrospective comparison of TISSEEL with non fibrin sealant from historical controls that reported CSF leaks following anterior base procedures or retromastoid craniectomy (RMC) procedures.

The researchers estimated that if TISSEEL had been applied to all 253 cases in their analysis, a cost savings of at least $75,151 would have been realized. (See figure below for cost per treatment.) The researchers concluded that TISSEEL use in dural closing, even when applied to every case, is highly cost-beneficial when compared to the cost of CSF repair.

Figure 6: Total costs for TISSEEL and control groups (Kassam, 2003)



Differences in outcome event rates reported by Kassam et al. that were used in the budget impact model are reproduced in the table below.

Table 14: Outcome differences between TISSEEL and historical controls (Kassam, 2003)

	TISSEEL	No Fibrin Sealant
N=	72	181
Proportion treated with fibrin sealant	100.0%	0.0%
Number of patients with CSF leak	0	10
Case rate with CSF leak	0.0%	5.5%
Proportion of cases no leak	100.0%	94.5%
Requiring surgical repair	0	4
Rate of surgical repair	0	2.2%

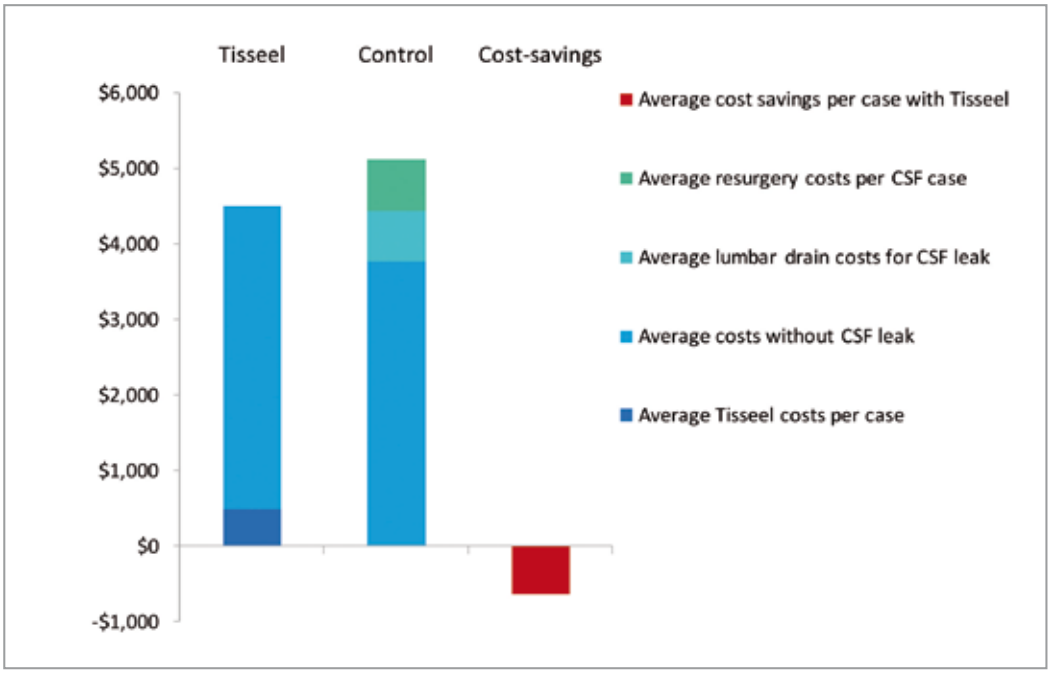
The estimated disaggregated costs (average costs per case) for TISSEEL and no fibrin-sealant in the US when used in neurosurgical procedures are described below.

Table 15: Estimated costs for TISSEEL vs. control in neurosurgical procedures

	TISSEEL	No Fibrin Sealant
Average TISSEEL costs per case	$500.00	$0.00
Average costs without CSF leak	$4,000.00	$3,779.01
Average lumbar drain costs for CSF leak	$0.00	$662.98
Average re-surgery costs per CSF case	$0.00	$685.46
Average cost per case	$4,500.00	$5,127.45
Average cost savings per case when using TISSEEL		-$627.45

The average cost per neurosurgical repair case and cost-savings achieved using TISSEEL are shown in the figure below.

Figure 7: Cost per patient per neurosurgical procedure (Kassam, 2003)



Budget Impact - Gastric Bypass Surgery

Leaking anastomoses are an important adverse event associated with gastrointestinal procedures. Although leak rates can average between 2-4%, they are an important AE because of the high costs associated with repair, as well as with associated morbidity and mortality. Use of TISSEEL under these conditions is ideal because of its sealant properties and ability to control bleeding.

Adverse event rates following gastric by-pass surgery, along with treatment cost consequences, were compared between two studies described in the table below (Fernandez, 1996; Silecchia, 2008).

Table 16: Summary of gastric bypass trials used in the combined analysis

	Fernandez, 1996	Silecchia, 2008
Study design	Prospective, randomized controlled trial	Prospective, multicentered, randomized clinical trial
Indication	Gastrectomy for gastric adenocarcinoma	Morbid obesity
Surgical procedure	Roux-en-Y jejunal loop	Roux-en-Y gastric bypass
Treatment comparison	TISSEEL compared with no fibrin sealant	TISSEEL compared with sutures without sealant
Patients recruited	N=86	N=320
Location	Spain	France, Italy

The budget impact model in gastric bypass is based on differences in treatment failure reported from the combined analysis of the Fernandez and Silecchia trials (Fernandez, 1996; Silecchia, 2008).

The differences in events from the meta-analysis on which the costs are based are shown in the table below.

Table 17: Outcomes utilized in gastric by-pass budget impact model

	TISSEEL	Placebo
Percentage bypass surgeries leaking anastomosis†	0.50%	5.39%
Percent bypass surgeries no leaking	99.50%	94.61%
TISSEEL use		
2mL	50%	0%
5mL	50%	0%

†Leaking anastomosis rate is based on event rates derived from a meta-analysis presented in a separate report.

Based on the anastomosis leak event rate probabilities for both TISSEEL and no fibrin-sealant use, we can derive an average cost per case for each treatment. The average cost per case for TISSEEL also includes acquisition costs for TISSEEL which are €318.47 on average per case. However, these costs are more than made up for by reduced anastomosis events. The cost-savings achieved with using TISSEEL is approximately €1,641 per case. These results are dependent on similar anastomosis leak event rates observed in Spain.

Table 18: Estimated costs for using TISSEEL vs. control during gastric bypass

	TISSEEL	No Fibrin Sealant
Average TISSEEL costs per patient	€318.47	€0.00
Average hospitalization cost per case for no leak cases	€6,006.12	€5,710.53
Average hospitalization cost per case for leaking anastomosis	€228.04	€2,483.87
Average cost per case†	€6,553	€8,194
Average cost savings per case when using TISSEEL		- €1,641

†Average budget impact per case with and without anastomosis leak based on use of TISSEEL or no sealant

Budget Impact - Incisional Hernia Repair

Previous studies have shown that TISSEEL improves surgical repair of incisional hernias by decreasing morbidity and duration of hospital stays. For example, Canonico et al. reported that patients with coagulation problems undergoing Lichtenstein inguinal hernia repair reported that the cost of care with TISSEEL was US$5600 (Canonico, 1999). Patients without TISSEEL use were more likely to have prolonged stays, and had an average cost of US$23,000.

Lobato et al. conducted a prospective randomized study of TISSEEL use in dermolipectomy and incisional hernia repair in Spain (Lobato, 2001). The researchers reported that largely due to blood transfusion and hospital stay, the total cost of care was US$68,182 for the TISSEEL group and US$82,005 for the control, demonstrating a cost-benefit to TISSEEL use with a cost savings of US$460 per patient.[8] Details of the cost analysis are shown in the table below.

To reflect the cost differences between these products, a budget impact model was constructed taking into consideration differences in primary and secondary outcomes with TISSEEL or in the absence of fibrin sealant. The effectiveness of TISSEEL use in incisional hernia was reported by Lobato et al. (Lobato, 2010). The study collected morbidity data and resource use data for each procedure. Costs were published in the original Lobato study; however, the example shown here is based on updated costs from Spain in 2009. The morbidity and adverse events as reported are shown in the table below.

Table 19: Economic analysis of incisional hernia repair (Lobato, 2001)

	Control (n=30)	TISSEEL (n=30)
Hospital stay	US$81,334 (€97,524)	US$65,536 (€77,056)
Blood transfusion	US$671 (€792)	0
TISSEEL	0	US$2,646 (€3,090)
Total cost	US$82,005 (€98,316)	US$68,182 (€80,146)

In a 2010 presentation at the American Society of Health System Pharmacists, Lobato et al. updated costs of incisional hernia repair in a budget impact model, inputting Spanish costs from the hospital perspective (Lobato, 2010). The analysis demonstrated the potential cost savings to the hospital with the use of TISSEEL at approximately €5462 per case.

Based on reported treatment costs in Spain, we estimate the average cost per case for performing incisional hernia with TISSEEL compared with no fibrin sealant. The cost estimate includes the frequency of morbid events for both treatments to reflect these costs in the average cost per surgical procedure. The disaggregated cost items in incisional hernia and cost-savings achieved using TISSEEL are shown in the table below.

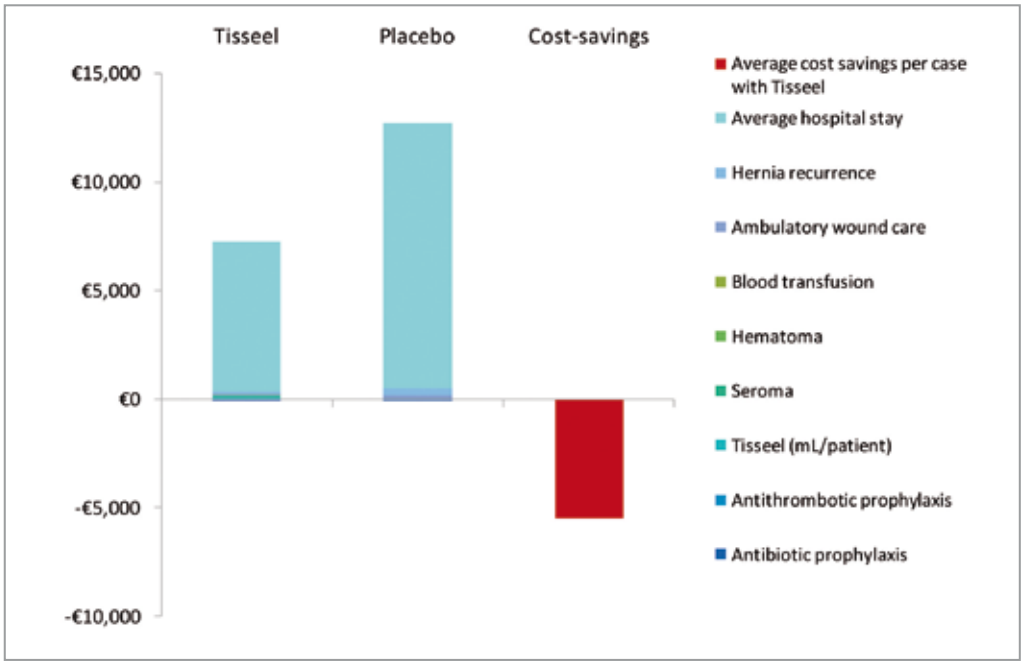
8 The large cost differences in the Canonico et al. and Lobato et al. study may have multiple explanations. Canonico et al. published in 1999, while Lobato et al. published in 2001. Neither study reported the year in which they were valuing costs, but inflation over these 12 years could account for some of the difference. In addition, Canonico et al.'s TISSEEL and control patients were hospitalized, on average, 1 and 7 days, respectively. In the Lobato et al. study, TISSEEL and control patients had much longer average hospitalizations – 7 and 12.6 days, respectively. Furthermore, Canonico et al.'s studied inguinal hernia repair, while Lobato et al. looked at incisional hernia repair.

Table 20: Estimated costs for using TISSEEL vs. Control

	TISSEEL	Placebo
Antibiotic prophylaxis	€1.80	€1.80
Antithrombotic prophylaxis	€18.34	€18.34
TISSEEL (mL/patient)	€179.58	€0.00
Seroma	€1.70	€1.14
Hematoma	€0.89	€2.66
Blood transfusion	€0.00	€43.09
Ambulatory wound care	€45.02	€156.58
Hernia recurrence	€140.25	€284.75
Average hospital stay	€6,895.38	€12,236.87
Average cost per case	€7,283	€12,745
Average cost savings per case using TISSEEL		-€5,462

The average cost per incisional hernia case and the disaggregated costs are shown in the figure below. The costs are mostly attributed to hospitalization.

Figure 8: Cost per patient per procedure for TISSEEL vs. control in incisional hernia repair (Baxter data on file)



Summary of Findings

Research studies have demonstrated not only the efficacy and safety of TISSEEL, but also additional clinical, economic, and humanistic value. A review of the literature reveals that TISSEEL may be associated not only with improved hemostasis, reduced blood loss, and reduced blood transfusions, but also with a reduction in healthcare resource utilization such as operating time, surgical revision, and length of hospital stay; a reduction in complications, such as seroma formation and fluid leakage; a reduction in pain and improved quality of life; and a reduction in costs. A review of findings referenced in this document is provided in Appendix D: Summary of Evidence Comparing TISSEEL to Other Products and/or Methods.

Appendix A: Competitive Comparison

The properties of the sealant and clot are affected by the concentration of fibrinogen and thrombin. The mechanical strength of the fibrin clot is influenced by the concentration of fibrinogen, Factor XIII, and adhesive proteins administered. Higher concentrations of fibrinogen tend to form stronger clots, whereas higher concentrations of thrombin tend to form clots more rapidly (Albala, 2003).

EVICEL

EVICEL fibrin sealant is an all-human, aprotinin-free fibrin sealant indicated for hemostasis.[9] It is available in spray or drip applications, and requires thawing prior to use. EVICEL is used to support surgery when standard surgical techniques are insufficient, for hemostasis improvement, and also as suture support for hemostasis in vascular surgery. TISSEEL differs from EVICEL in several ways. First, in vitro, there are differences in ultrastructure and alpha-chain cross-linking rates, which lead to a significantly enhanced sealing efficacy as evidenced in vivo (Hedrich, 2012). In addition, total clot lysis is shorter with EVICEL clots, compared to TISSEEL (2 vs. 5 days, respectively), and a statistically significant lower leakage pressure is obtained with pooled lots of EVICEL, compared to TISSEEL (two-sided, $p<0.0001$).

Moreover, after thawing, TISSEEL requires no additional preparation, and is ready to use, unlike EVICEL which requires 10 minutes plus prep time.[10,11] Finally, when sprayed, TISSEEL provides five times the coverage that EVICEL provides. (See table below.)

Table 21: Comparison of coverage between TISSEEL and EVICEL

TISSEEL Size	TISSEEL Coverage	EVICEL Size	EVICEL Coverage
2 mL	100 cm^2	1 mL	20 cm^2
4 mL	200 cm^2	2 mL	40 cm^2
10 mL	500 cm^2	5 mL	100 cm^2

Sources: TISSEEL Full Prescribing Information, 2012. EVICEL (Fibrin Sealant) Full Prescribing Information, 2009.

TACHOSIL

TACHOSIL is a ready-to-use surgical patch that promotes hemostasis and tissue sealing.[12] It contains a fixed combination of a patch sponge coated with a dry layer of the human coagulation factors fibrinogen and thrombin. TACHOSIL is indicated for supportive treatment in surgery to improve hemostasis, to promote tissue sealing, and for suture support in vascular surgery when standard techniques are not sufficient. TISSEEL fibrin sealant differs from TACHOSIL in that it can be sprayed, and used with a wide variety of application devices. This makes TISSEEL more ideal for minimally-invasive and open procedures.[13] In addition, TACHOSIL is a sponge that can stick to instruments or gloves and is challenging to apply in laparoscopic procedures. Finally, TISSEEL provides more coverage than TACHOSIL provides. (See table below.)

Table 22: Comparison of coverage between TISSEEL and TACHOSIL

TISSEEL Size	TISSEEL Coverage	TACHOSIL Size	TACHOSIL Coverage
2 mL	100 cm^2	3.0 cm x 2.5 cm (1 sponge)	7.5 cm^2
4 mL	200 cm^2	3.0 cm x 2.5 cm (5 sponges)	37.5 cm^2
10 mL	500 cm^2	9.5 cm x 4.8 cm (1 sponge)	45.6 cm^2
10 mL	500 cm^2	4.8 cm x 4.8 cm (2 sponges)	46.1 cm^2

Sources: TISSEEL Full Prescribing Information, 2012. TACHOSIL Summary of Product Characteristics, 2009.

9 Ethicon data on file. www.ethicon360.com/products/EVICEL-fibrin-sealant-human. Accessed January 10, 2013.
10 TISSEEL Full Prescribing Information, 2012.
11 EVICEL (Fibrin Sealant) Full Prescribing Information, 2009.
12 Takeda Pharmaceuticals. http://www.TACHOSIL.com/productdetails.
13 Also see DUPLOSPRAY MIS Instructions for Use; PN21281, Rev A. and EASYSPRAY Set Instructions for Use; 6208400EH07, 2005.

In summary, TISSEEL is the only '4 in 1' fibrin sealant, promoting hemostasis, sealing, adherence, and healing. Its unique formulation increases elasticity of the fibrin clot, tensile strength, and adhesive strength than its comparators. Other advantages to TISSEEL use are summarized in the table below.

Table 23: Summary of Advantages in TISSEEL versus EVICEL and TACHOSIL

Product Features	TISSEEL	EVICEL	TACHOSIL
4 in 1 product: hemostasis, sealing, adhesion, and healing	•		
Available in a pre-filled and pre-mixed syringe (frozen)	•		
Full range of applicators available	•		
Ease of use in minimally-invasive surgery	•	•	
Can be sprayed	•	•	
Contains a synthetic clot stabilizer	•		
Maximum amount of commercially-available fibrinogen	•		
Does not swell	•	•	•

Sources: TISSEEL Full Prescribing Information, 2012. EVICEL (Fibrin Sealant) Full Prescribing Information, 2009. TACHOSIL Summary of Product Characteristics, 2009.

Appendix B: The Use of Aprotinin

Aprotinin is a critical element in TISSEEL fibrin sealant. TISSEEL is the only sealant and hemostat in the US containing aprotinin as an anti-fibrinolytic agent to preclude premature clot lysis, thereby extending the life of the clot when the natural process of fibrinolysis or hyperfibrinolytic surgical situations (e.g., surgeries involving cardiopulmonary bypass or trauma) might otherwise threaten clot lysis. In pre-clinical studies, the addition of aprotinin to TISSEEL was demonstrated to improve clot persistence (Pfluger, 1986). Using aprotinin extends the life of the physiologic clot created by the fibrin sealant, thereby allowing time for the body's natural healing processes to occur (Pipan, 1992). In addition, in vitro and in vivo studies have shown that aprotinin-free fibrin sealant degrades significantly faster than sealants containing aprotinin (Pipan, 1992; Pfluger, 1986). No competing fibrin sealant available in the US provides this combination; however, aprotinin is used in competitor products available outside of the US. The presence of aprotinin prevents premature clot lysis and extends the life of the clot (Pfluger, 1986).

Aprotinin Hypersensitivity: Systemic Versus Local Application

Systemic aprotinin (i.e., administered intravenously) has been in clinical use for nearly 40 years as a fibrinolytic to inhibit fibrinolysis and preserve platelet function. When used systemically, aprotinin has been shown to reduce blood loss and transfusion requirements in cardiac surgery, lung and liver transplantations, and surgery for hip replacement. Primary exposure to aprotinin has been shown to be safe; increasingly, however, concerns have been raised regarding hypersensitivity to aprotinin following re-exposure. Although hypersensitivity events are rare, it has been suggested that the risk in the subgroup of re-exposed patients is approximately 1.2% to 2.7% (Dietrich, 1998). Furthermore, it has been shown that 95% of all reactions upon re-exposure occurred within 36 months (Beierlein, 2005).

Despite the limited risks associated with re-exposure, in 2007 the European Medicines Agency (EMEA) recommended suspending the marketing authorization of aprotinin-containing medicines for systemic use (EMEA, 2007). However, "a review from the EMEA's Committee for Medicinal Products for Human Use (CHMP), published February 17, 2012, found a number of faults with how the BART study was conducted, and that its results could not be replicated in further investigations."[14] Health Canada, the healthcare regulator for Canada, also lifted its suspension of Trasylol in 2011. **Most importantly, this warning does not apply to TISSEEL Fibrin Sealant as it is locally, not systemically, applied; therefore TISSEEL does not carry the same risk as those attributed with systemic administration.**

Furthermore, the risks associated with aprotinin are thought to be dose-dependent and the doses of aprotinin in TISSEEL are below those with associated risks. The investigations by Mangano et al. have shown that doses exceeding 2 million kallikrein-inhibitor units [KIU] per mL, considered to be high-dose aprotinin, were associated with renal dysfunction and cardiac events compared with low-dose aprotinin and control subjects (Mangano, 2006). In contrast, TISSEEL is administered topically within a fibrin clot at a dosage of 2250-3750 KIU/mL. As a result the recommended topical dose of aprotinin in TISSEEL is <1% of the usual intravenous aprotinin dose, suggesting the risks are minimal compared with intravenous administration.

Aprotinin plays a vital role in the functional efficacy of TISSEEL. **Without aprotinin, the fibrin clot could be lysed within hours rather than days, especially in hyperfibrinolytic conditions that may arise during or after major surgery.** The local mass of solidified fibrin sealant is ultimately completely absorbed during the course of the body's natural wound healing process. Consequently, limited amounts of aprotinin actually enter into the blood stream. Furthermore, the kidney eliminates any released aprotinin and its metabolites. The half-life of aprotinin in blood is known to average between 30 and 60 minutes.

Since concerns were raised about the possibility of hypersensitivity to aprotinin, numerous studies have explored the consequences of repeated exposure to aprotinin. One such study conducted in pediatric heart surgery patients concluded that reactions were no more likely on second, third, or higher exposure to aprotinin than on initial exposure (Jaquiss, 2002). However, other investigations have suggested the risks of repeated exposure are inconclusive (Oswald, 2003).

14 PMLive Release: EMA recommends lifting suspension of Bayer's Trasylol. http://www.pmlive.com/pharma_news/ema_recommends_lifting_suspension_bayer_trasylol_371658.

Users of this document should be aware that aprotinin is not the subject of this dossier. Persons looking for guidance on aprotinin risks should consult local and international sources.

Appendix C: TISSEEL Product Details

Manufacturing and Delivery

TISSEEL is made from human plasma; consequently it carries a theoretical risk of transmitting plasma pathogens (e.g., viruses, Creutzfeldt-Jakob disease). Three major programs and developments have been introduced to assure the safety of modern plasma-derived blood products. These consist of (1) donor-selection procedures, (2) serologic testing for viral contaminants, and (3) viral inactivation by vapor heating and solvent/detergent treatment. Each safety element is briefly described.

Plasma used in TISSEEL manufacturing is obtained from donors who are prequalified through a comprehensive screening procedure. Following the establishment of a case history (including a physical examination), potential donors are entered into the plasma screening program. The donor selection system is designed to identify and retain highly motivated repeat donors. A remuneration system compensating for time and expenses contributes to the high percentage of reliable repeat donors.

Serologic testing of plasma pools is conducted in coordination with inventory management of blood from pre-screened donors to reduce the acceptance of contaminated blood even before viral inactivation.

The manufacturing procedure for TISSEEL includes processing steps designed to reduce the risk of viral transmission, including vapor heating and solvent/detergent treatment processes.

In the production of all plasma-derived therapeutics, including fibrin sealant, pathogen safety is of paramount importance at Baxter Healthcare. Through its Global Pathogen Safety Group, **Baxter is a world leader in all aspects of plasma-derived therapeutic safety** from initial donor selection to final product formulation.[15] Baxter is Q-SEAL certified by the Plasma Protein Therapeutics Association (PPTA) and **has adopted voluntary standards that go beyond regulatory requirements** and helped define the regulations as they apply to fractionation of plasma for plasma therapeutics.[16]

The intrinsic pharmacological properties of TISSEEL's active ingredients—fibrinogen, thrombin, calcium chloride, and aprotinin—are unaltered by the manufacturing, reconstitution, and surgical delivery processes. The basic pharmacology of a clinically applied fibrin sealant product such as TISSEEL is analogous to the physiological processes of blood clotting. This fibrin sealant when used clinically is essentially a unique pharmaceutical form of locally applied, locally acting, and locally metabolized medicinal product.

In 2007, TISSEEL VH S/D was introduced as the next generation fibrin sealant which may eventually replace the vapor-heated (VH) formulation. The sole critical difference in the next generation formulation is the addition of a solvent/detergent ("S/D") virus inactivation step to provide added safety to the previous product. A Phase III, prospective, randomized, double-blind multicenter study was performed to prove there was no difference in efficacy and safety between the TISSEEL VH and TISSEEL VH S/D formulations during cardiac surgery (Lowe, 2007).

Administration and Dosage Forms

TISSEEL components are mixed immediately prior to use to give two reconstituted solutions in separate containers ready for application using an appropriate delivery system or device.

Several different TISSEEL Fibrin Sealant delivery systems and dosage forms are available to meet the range of surgical needs in different settings. TISSEEL Fibrin Sealant is available in two presentations—frozen and lyophilized—which are packaged into three different product configurations. Each individual package provides all of the components required to prepare and deliver the fibrin sealant product. Minor variations in preparations and application may exist, however, when prepared according to the product preparation guidelines, all products work identically in mimicking the final stages of the coagulation cascade.

15 Baxter Pathogen Safety Monograph.
16 Plasma Protein Therapeutics Association

Using the United States as an example, the following table summarizes differences in product formulations and application devices.

Table 24: Differences in product formulation and application devices

Product	TISSEEL VH Lyophilized	TISSEEL VH S/D Lyophilized	TISSEEL VH S/D Frozen
Introduction date	1978	February 2007	May 2007
Viral Inactivation	Vapor-heating	Vapor-heating Solvent/detergent	Vapor-heating Solvent/detergent
Packaging	Vials, Duploject syringe	Vials, Duploject syringe	Prefilled syringe
Preparation	Reconstitution Warming	Reconstitution Warming	Thawing/Warming
Antifibrinolytic	Bovine aprotinin	Synthetic aprotinin Bovine aprotinin (phasing out)	Synthetic aprotinin Bovine aprotinin (phasing out)

TISSEEL Fibrin Sealant is indicated as both a sealant and a hemostat, and, thus, requires different application techniques in order to meet all possible situations in which it is likely to be used. TISSEEL can be used with a full range of spray systems and application delivery devices, providing flexibility to apply TISSEEL exactly how, where, and when it is required. As explained in the TISSEEL Prescribing Information (12/2007), the EASYSPRAY system allows coverage of broad surface areas in open surgical procedures with maximum product utilization (500 cm^2 per 10 mL kit), while the DUPLOSPRAY system provides a similar thin, uniform layer of fibrin sealant in endoscopic procedures. Several different administration techniques are available with TISSEEL to meet the needs of surgeons and patients in different surgical procedures. Regardless of the administration or formulation, TISSEEL is designed to mimic normal physiological blood clotting.

During administration, the sealant is administered by applying a thin even layer over the exposed tissue. The amount of TISSEEL applied depends on a variety of factors including the type of surgery, the surface area of the tissue to be treated, and the way it is applied. Please refer to Appendix E at the end of this document for full prescribing and application information.

Appendix D: Summary of Evidence Comparing TISSEEL to Other Products and/or Methods

Table 25: Summaries of studies comparing TISSEEL to other products/methods

Specialty	Type of Surgery	Author, Year	Intervention & Comparator (N)	Patient Population	Research Design	Results (TISSEEL Results Bolded)	Supported Value Message
Cardiac and Vascular	Cardiac	Kieser, 1995	TISSEEL (N=200; 2 groups of 100 patients undergoing surgery at different times) No TISSEEL (N=100)	Patients undergoing aortic coronary bypass and/or valve surgery at one site in Canada	Retrospective chart review	• Number of blood units transfused: **10.3-13.2 U** vs. 23.7 U (p<0.01) • Patients not requiring transfusion: **33.3-38.1%** vs. 10.4% (p<0.01) • Patients requiring reoperation for bleeding: **5.2-7.3%** vs. 21.8% (p<0.01)	• Less resource utilization
	Cardiac	Rousou, 1989	TISSEEL (N=164) Surgeon choice of conventional topical agent (N=169)	Patients undergoing cardiac reoperation and resternotomy at 11 US centers	Randomized, multicenter	• Hemostasis at 5 minutes: **92.6%** vs. 12.4% (p<0.001) • Successful hemostasis - Redo for CAD: **93%** vs. 12%, p<0.001 - Noncoronary cardiac disease: **92%** vs. 13%, p<0.001	• Rapid hemostasis and less blood loss
	Cardiac	Martinelli, 1995	TISSEEL + aprotinin (N=145) No TISSEEL (N=116)	Patients undergoing heart transplantation at one site	Retrospective review	• Blood collected from the field: 55 mL vs. 250 mL (p<0.001)	• Less resource utilization
	Vascular	Saha, 2011	TISSEEL with clamps open at 60 seconds (N=26) and 120 seconds (N=24) Manual compression (N=23)	Patients undergoing vascular surgery and receiving prosthetic ePTFE vascular grafts in the US	Prospective, randomized, controlled, subject-blinded, multicenter	• Hemostasis at 4 min: **62.5% (Tiss-120)** vs. 34.8% (79.6% relative improvement)	• Rapid hemostasis and less blood loss
	Vascular	Saha, 2012	TISSEEL (N=70) Manual compression (N=70)	Patients undergoing vascular surgery and receiving prosthetic ePTFE vascular grafts in 24 US centers	Prospective, randomized, controlled, subject-blinded, multicenter	• Hemostasis at 4 min: **67.1%** vs. 31.4% • Additional hemostasis treatment required: **18.6%** vs. 40.0% • Hemostasis at 4 min, maintained until closure: **62.9%** vs. 31.4% (p<0.0001) • Hemostasis at 6 min: **71.4%** vs. 42.9% (p=0.001) • Hemostasis at 10 min: **75.7%** vs. 55.7% (p=0.012)	• Rapid hemostasis and less blood loss

Specialty	Type of Surgery	Author, Year	Intervention & Comparator (N)	Patient Population	Research Design	Results (TISSEEL Results Bolded)	Supported Value Message
Neuro/Spinal	Calvarial remodelling for sagittal synostosis	White, 2009	TISSEEL (N=6) No TISSEEL (N=10)	Patients treated surgically by calvarial remodelling for single suture sagittal synostosis in the UK	Prospective	• 8 hour drain: **172** vs. 246 mL (p<0.02) • Total drain volume: **301** vs. 441 mL (p<0.01) • Transfusion: **0%** vs. 20% (p<0.02)	• Less resource utilization
	Multilevel anterior cervical fusion	Yeom, 2008	TISSEEL (N=30) No TISSEEL (N=30)	Patients undergoing multilevel anterior cervical fusion in one US center	Retrospective matched pair analysis	• Drain output: **47** vs. 98 mL (p<0.0001) • Time to drainage: **17** vs. 24 hrs (p=0.0054) • LOS: **1.2** vs. 2.1 days (p<0.0001)	• Less resource utilization
	Neurosurgical procedures	Kassam, 2003	TISSEEL (N=72) No TISSEEL (N=181)	Patients undergoing anterior cranial base, infratemporal, and retromastoid surgical procedures at one US center	Retrospective chart review of two matched cohorts	• CSF leak rates: **0%** vs. 5.5% (p=0.067) • Cost estimates: - If CSF leak pts treated with TISSEEL: **$90,500** - Cost without TISSEEL: $165,651 • Est cost savings: $75,151	• Less resource utilization • Cost savings
General (Hernia Repair)	Inguinal hernia repair	Benizri, 2006	TISSEEL (N=57) Sutures (N=57)	Patients undergoing hernia surgery in France	Case-control matched	• Operation time: **44** vs. 54 min in unilateral hernia (p=0.0017), **82** vs. 98 min in bilateral hernia (p=0.00018) • Length of stay: **1.8** vs. 2.4 days (p<0.0001) • Chronic inguinal pain: **3.5%** vs. 22.8% (p=0.042)	• Less resource utilization • Less pain and better QoL
	Inguinal hernia repair	Campanelli, 2012	TISSEEL (N=159) Sutures (N=160)	Patients undergoing hernia surgery in 7 centers in 7 European countries	Randomized, controlled, double-blinded	• Moderate-to-severe pain at 12 months: **8.1%** vs. 14.8% (p=0.0344) • Use of pain medications: **65.2%** vs. 79.7% (p=0.0009)	• Less pain and better QoL
	Inguinal hernia repair	Canonico, 1999	TISSEEL (N=25) No TISSEEL (N=25)	Patients with coagulation disorders undergoing Lichtenstein hernia repair in Italy	Prospective, randomized, controlled	• Post-operative hemorrhagic complications: **4%** vs. 24% (p=0.049) • Hospital discharge <24 hrs: **100%** vs. 76% • Total costs: **US$5600** vs. US$23,000	• Rapid hemostasis and less blood loss • Less resource utilization • Cost savings
	Inguinal hernia repair	Ceccarelli, 2008	TISSEEL (N=68) Staples (N=68)	Patients undergoing TAPP in Italy	Case-control	• Pain at 10mm trocar site: **0%** vs. 5.9%, p<0.05	• Less pain and better QoL
	Inguinal hernia repair	Fortelny, 2012	TISSEEL (N=44) Staples (N=45)	Patients undergoing TAPP with unilateral and bilateral hernias	Prospective, randomized, controlled	• Time to significant physical health score increase: **3** vs. 12 mo • Time to significant mental health score increase: **3 mo** (no increase in control group)	• Less pain and better QoL

Specialty	Type of Surgery	Author, Year	Intervention & Comparator (N)	Patient Population	Research Design	Results (TISSEEL Results Bolded)	Supported Value Message
General (Hernia Repair)	Inguinal hernia repair	Hidalgo, 2005	N=55 Left side: TISSEEL Right side: stiches	Patients undergoing Lichtenstein bilateral hernia repair in Italy	Prospective, randomized	• Pain reported: - None: **80%** vs. 32% - Mild: **18%** vs. 47.2% - Moderate: **1.8%** vs. 25.4%	• Less pain and better QoL
	Inguinal hernia repair	Kaul, 2012	TISSEEL: 268 repairs Staples or tacks: 394 repairs	Four studies with patients undergoing inguinal hernia repair	Meta-analysis	• Chronic inguinal pain at 3 months: significantly higher with staple/tack fixation (OR 3.25; 95% CI 1.62-6.49)	• Less pain and better QoL
	Inguinal hernia repair	Lau, 2005	TISSEEL (N=46) Staples (N=47)	Patients undergoing TEP bilateral inguinal hernia repair	Prospective, randomized	• Analgesic medication consumed: **4.5** vs. 7 tablets (p=0.034)	• Less pain and better QoL
	Inguinal hernia repair	Lovisetto, 2007	TISSEEL (N=99) Staples (N=98)	Patients undergoing laparoscopic TAPP repair of inguinal and femoral hernias	Prospective, randomized	• Time to resumption of normal activities: **7.9** vs. 9.1 days (p<0.001) • VAS scores: - 1 mo: **19** vs. 26 mm (p<0.05) - 3 mo: **11** vs. 23 mm (p<0.001) - 6 mo: **11** vs. 20 mm (p<0.001) • SF-36 scores at 1 month: TISSEEL had lower morbidity, quicker return to work and social life (p<0.05)	• Less pain and better QoL
	Inguinal hernia repair	Negro, 2011	TISSEEL (N=349) Sutures (N=171)	Patients undergoing Lichtenstein hernia repair in 16 centers in Italy	Prospective, observational	• Operating time: **55.6** vs. 61.2 min (p<0.001) • Patients reporting numbness: **12.3%** vs. 23.4% (p=0.003) • Mean pain score: **2.5** vs. 3.2 (p<0.001) • Intense pain score: **0.6** vs. 1.2 (p=0.001)	• Less resource utilization • Less pain and better QoL
	Inguinal hernia repair	Olmi, 2007	TISSEEL (N=150) Protak (N=150) EndoANCHOR (N=150) EMS (N=150)	Patients undergoing laparoscopic TAPP hernioplasty (uni- and bilateral) in Italy	Prospective, randomized	• Pain rated as lowest in severity in TISSEEL group • Operating time: **uni-30min, bi-50min** vs. uni-35-38min, bi-52-55min (p<0.05) • Hospitalization time: **1.0 day** vs. 1.1-1.2 days (p<0.05) • Time to resumption to work: **5 days** vs. 7-9 days (p<0.05)	• Less resource utilization • Less pain and better QoL
	Inguinal hernia repair	Schwab, 2006	TISSEEL (N=86) Staples (N=87)	Patients undergoing TEP unilateral and bilateral inguinal hernia repair in a single center in Germany	Retrospective case control	• Prevalence of chronic inguinal pain: **4.7%** vs. 20.7% (p=0.002) • Persistent foreign body sensation: **1.2%** vs. 5.7% (p>0.05)	• Less pain and better QoL

Specialty	Type of Surgery	Author, Year	Intervention & Comparator (N)	Patient Population	Research Design	Results (TISSEEL Results Bolded)	Supported Value Message
General (Hernia Repair)	Inguinal hernia repair	Testini, 2010	TISSEEL (N=52) Sutures (N=59) Glubran 2 (N=56)	Patients undergoing surgery for groin hernia repair in an academic institution in Italy	Prospective, randomized, controlled	• Overall morbidity rate: **9.62%*** vs. 38.98%* (sutures) vs. 10.71% (Glubran) [*p<0.001] • Moderate chronic pain: **0%*** vs. 3.39%* (sutures) vs. 9% (Glubran) [*p=0.01] • Extraneous body sensation: **0%*** vs. 8.74%* (sutures) vs. 1.78% (Glubran) [*p=0.01] • Long-term complications: **0%*** vs. 11.86%* (suture) vs. 1.78% (Glubran) [*p=0.01]	• Less pain and better QoL
	Inguinal hernia repair	Topart, 2005	TISSEEL (N=66) Staples (N=102)	Patients undergoing TEP unilateral and bilateral hernia repair in France	Retrospective cohort analysis	• Chronic pain rate: **4.5%** vs. 14.7% (p=0.037)	• Less pain and better QoL
	Incisional hernia repair	Lobato, 2001	TISSEEL (N=30) No TISSEEL (N=30)	Patients undergoing incisional hernia repair in Spain	Prospective, randomized	• Blood transfusion: **0%** vs. **13.3%** (p<0.001) • Cellulitis: **3.3%** vs. 20% (p<0.01) • Hematoma: **6.6%** vs. 20% (p<0.01) • LOS: **7.1** vs. 12.6 days (p<0.01) • Total cost: **US$68,182** vs. US$82,005	• Less resource utilization • Cost savings
	Incisional hernia repair	Lobato, 2010	TISSEEL (N=30) No TISSEEL (N=30)	Patients undergoing incisional hernia repair in Spain	Cost data applied to prospective, randomized study	• Hospital cost: **€6895** vs. €12,237 • Total cost: **€7284** vs. €12,744	• Cost savings
Gynecology	Myomectomy	Angioli, 2012	TISSEEL (N=15) No TISSEEL (N=15)	Patients undergoing myomectomy in Italy	Case-control	• Time to hemostasis: **195.5** vs. 361.8 sec (p<0.0001) • Blood loss: **111.3** vs. 230 mL (p<0.05) • Operating time: **47.7** vs. 62.1 min (p<0.05)	• Rapid hemostasis and less blood loss • Less resource utilization
ENT	Pariotidectomy	Maharaj, 2008	TISSEEL (N=28) No TISSEEL (N=22)	Patients undergoing superficial or total parotidectomy in Canada	Prospective, randomized, controlled	• Wound drainage: **41.3** vs. 65.3 mL (p<0.02) • Seroma formation: **3.6%** vs. 22.7% (p<0.05)	• Less resource utilization
	Thyroidectomy	Uwiera, 2005	TISSEEL (N=28) No TISSEEL (N=22)	Patients undergoing total or hemithyroidectomy in Canada	Prospective, randomized, controlled, blinded	• Wound drainage: **30.9** vs. 55.1 mL (p<0.001) - Hemi: **27.1** vs. 53.4 mL (p<0.001) - Total: **34.5** vs. 54.3 mL (p<0.001)	• Less resource utilization

Specialty	Type of Surgery	Author, Year	Intervention & Comparator (N)	Patient Population	Research Design	Results (TISSEEL Results Bolded)	Supported Value Message
Surgery in Cancer	Axilllary lymph-adenectomy	Gilly, 1998	TISSEEL (N=50) No TISSEEL (N=58)	Patients undergoing axillary lymphadenectomy in breast cancer in France	Prospective, randomized	• Post-operative drainage: **214.4** vs. 407.8 mL (p=0.001) • LOS: **8.0** vs. 10.1 days (p=0.006)	• Less resource utilization
	Breast cancer surgery	Jain, 2004	No drain + TISSEEL (N=29) No drain (N=29) Drain (N=58)	Patients newly diagnosed with breast cancer undergoing primary excision and axillary lymphadenectomy	Prospective, randomized	• Of patients undergoing mastectomy, seroma formation: **42.1%** vs. 83.8% (no drain) [p=0.048]	• Less resource utilization
	Reconstructive operations	Fabrizio, 1995	TISSEEL (N=102) Control (N=112)	Patients undergoing prolonged reconstructive plastic interventions after ablative cancer surgery in one hospital in Italy	Prospective, randomized	• Dihescence: **4.8%** vs. 20.5% • Inflammation: **1.9%** vs. 14.7% • Scar hypertrophy: **11.7%** vs. 34.2% • LOS: **10.5** vs. 25 days	• Less resource utilization
Pediatric Surgery	Cardiac	Huth, 1983	TISSEEL vs. No TISSEEL ToF: **21** vs. 20 TGA: **10** vs. 10	Patients undergoing surgery for tetralogy of Fallot (ToF) correction and Senning-procedure in transposition of the great arteries (TGA) in Germany	Retrospective, controlled	• ToF bleeding (mL/hr/kg): 0-2 hrs: **2.2** vs. 4.2 (p<0.01) 3-6 hrs: **1.0** vs. 1.2 (p<0.05) 0-6 hrs: **1.4** vs. 2.2 (p<0.010) 0-12 hrs: **1.1** vs. 1.5 (p<0.05) • TGA bleeding (mL/hr/kg) : 0-2 hrs: **2.4** vs. 4.5 (p<0.01) 0-6 hrs: **1.9** vs. 2.5 (p<0.01) 0-12 hrs: **1.5** vs. 1.8 (p<0.05)	• Rapid hemostasis and less blood loss
	Esophageal surgery	Upadhyaya, 2007	TISSEEL (N=22) No TISSEEL (N=23)	Infants undergoing surgery for long-gap esophageal atresia with trach-eoesophageal fistula in India	Prospective, randomized, controlled	• Esophageal anastomotic leaks: **9.1%** vs. 43% (p=0.017) • Esophageal stricture: **10%** vs. 41% (p=0.028)	• Less resource utilization
	Resection surgery	Becker & Willital, 1994	TISSEEL vs. No TISSEEL Laser liver resection: **22** vs. 19 Kidney resection: **12** vs. 17 Pancreas resection: **20** vs. 34	Patients undergoing liver (laser), kidney, or pancreas resection	Retrospective, controlled	Liver resection: • Day 2 secretion volume: **15** vs. 30 mL • Day 3 secretion volume: **10** vs. 30 mL • Abscess: **0%** vs. 27.3% Kidney resection: • Bleeding: **8.3%** vs. 23.5% • Infection: **0%** vs. 52.9% • Urinary fistula: **0%** vs. **47.1%** Pancreas resection: • Bleeding: **0%** vs. 29.4% • Infection: **5.0%** vs. 35.3% • Urinary fistula: **10.0%** vs. 26.5%	• Rapid hemostasis and less blood loss • Less resource utilization

Specialty	Type of Surgery	Author, Year	Intervention & Comparator (N)	Patient Population	Research Design	Results (TISSEEL Results Bolded)	Supported Value Message
Pediatric Surgery	Hypospadias repair	Gopal, 2008	TISSEEL (N=60) No TISSEEL (N=60)	Patients undergoing surgical hypospadias repair in India	Prospective, randomized, controlled	• Edema: **16.7%** vs. 35.0% (p=0.039) • Fistula: **10.0%** vs. 31.7% (p=0.027) • Overall post-op complications: **20.0%** vs. 56.7% (p=0.003)	• Less resource utilization
	Dialysis catheter implantation	Sojo, 2004	TISSEEL (N=26) No TISSEEL (N=26) (52 catheters implanted in 45 children)	Patients receiving peritoneal dialysis catheters in Argentina	Prospective, randomized, controlled	• Dialysate leakage from catheter: **11%** vs. 54% (p<0.02) • Of early-used catheters, dialysate leakage: **9%** vs. 57% (p<0.05)	• Less resource utilization

Appendix E: TISSEEL IFU

This abbreviated summary of product characteristics (SPC) is intended for international use. Please note that it may differ from the licensed SPC in the country where you are practicing.
Therefore, please always consult your country-specific SPC or package leaflet.

TISSEEL or TISSUCOL

Fibrin Sealant
TISSEEL Lyo – Powders and solvents for sealant
TISSEEL – Solutions for sealant

COMPOSITION (after mixing), per 1ml

Component 1 (Sealer protein solution): Human fibrinogen (as clottable protein) 45.5mg, Aprotinin (synthetic) 1500 KIU
Component 2 (Thrombin solution): Human thrombin 250 IU, Calcium chloride 20 µmol

INDICATIONS

Supportive treatment where standard surgical techniques appear insufficient

- For improvement of hemostasis
- As a tissue glue to improve wound healing or to support sutures in vascular surgery, in gastrointestinal anastomoses, in neurosurgery and in surgical interventions where contact with cerebrospinal fluid or dura mater may occur (e.g. in ENT, ophthalmic and spinal surgery).
- For tissue sealing, to improve adhesion of the separated tissue (e.g. tissue flaps, grafts, split skin grafts [mesh grafts]).

The efficacy in fully heparinized patients has been proven.

CONTRAINDICATIONS

TISSEEL alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.
TISSEEL is not indicated to replace skin sutures intended to close surgical wound.
TISSEEL must never be applied intravascularly. Intravascular application may result in life-threatening thromboembolic events. TISSEEL must not be applied in case of hypersensitivity to the active substances or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For epilesional use only. Do not apply intravascularly. Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

Caution must be used when applying fibrin sealant using pressurized gas. Any application of pressurized gas is associated with a potential risk of air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening. Apply TISSEEL as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Life-threatening/fatal 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/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO2 and therefore cannot be excluded with TISSEEL when sprayed in open wound surgery. When applying TISSEEL using a spray device, be sure to use a pressure within the pressure range recommended by the spray device manufacturer. TISSEEL spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer. Do not spray closer than the recommended distances. When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO2 should be monitored because of the possibility of occurrence of air or gas embolism.

Tisseel must not be used with the Easy Spray/Spray Set sytem in enclosed body areas.

Before the administration of TISSEEL, care is to be taken that parts of the body outside the designated application area are sufficiently protected/covered to prevent tissue adhesion at undesired sites.

If fibrin sealants are applied in confined spaces, e.g. the brain or the spinal cord, the risk of compressive complications should be taken into account. To ensure adequate mixing of the sealer protein component and the thrombin component, the first few drops of the product from the application canula should be expelled and discarded immediately before use. As with any protein-containing product, allergic type hypersensitivity reactions are possible. Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients.

Hypersensitivity and anaphylactic reactions (also fatal, including anaphylactic shock) have been reported with TISSEEL. Signs of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension. If these symptoms occur, the administration must be discontinued immediately and the currently valid standard measures for the treatment of shock are to be taken. Remaining product must be removed from the site of application. TISSEEL contains a synthetic protein (aprotinin). Even in cases of strict local application, there is a risk of anaphylactic reaction linked to the presence of aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records. As synthetic aprotinin is structurally identical to bovine aprotinin the use of TISSEEL in patients with allergies to bovine proteins should be carefully evaluated. In two retrospective, non-randomized studies in coronary bypass surgery, patients who received fibrin sealant showed a statistically significant increased risk of mortality. While these studies could not provide a causal relationship, the increased risk associated with the use of TISSEEL in these patient's cannot be excluded. Therefore, additional care should be taken to avoid inadvertent intravascular administration of this product. Injection into the nasal mucosa must be avoided, as thromboembolic complications may occur in the area of the arteria ophthalmica.

Injecting TISSEEL into tissue carries the risk of local tissue damage.

TISSEEL should only be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process. Polysorbate 80 may cause locally limited skin irritations such as contact dermatitis. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens. These measures are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemolytic anemia). It is strongly recommended that every time TISSEEL is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. Oxidized cellulose-containing preparations should not be used with TISSEEL.

UNDESIRABLE EFFECTS

Hypersensitivity or allergic reactions (which may include but are not limited to angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, breathing difficulties, transient erythema [„flushing"], generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/hemostatics. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin or any other constituents of the product. Even if repeated treatment with TISSEEL was well tolerated, a subsequent administration of TISSEEL or systemic administration of aprotinin may result in severe anaphylactic reactions. Antibodies against components of

the fibrin sealant/hemostatic may occur in rare cases. Inadvertent intravascular injection may result in thromboembolic events and DIC. Furthermore there is the risk of an anaphylactic reaction. The following adverse reactions have been reported from clinical studies investigating the safety and efficacy of TISSEEL and from post-marketing experience with Baxter Fibrin Sealants:
Very common (>1/10): Seroma
Common (> 1/100 to < 1/10): Postoperative wound infection, sensory disturbance, anxillary vein thrombosis, rash, pain in an extremity, Pain, and increased body temperature.
Uncommon (>1/1,000 to <1/100): Fibrin degradation products increased, nausea, procedural pain.

Class Reactions
Other adverse reactions associated with the fibrin sealant/hemostatic class include: air or gas embolism when using devices with pressurized air or gas; 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. Manifestations of hypersensitivity include application site irritation, chest discomfort, chills, headache, lethargy, restlessness, and vomiting.

METHOD OF ADMINISTRATION
The use of TISSEEL is restricted to experienced surgeons who have been trained in its use of TISSEEL. In order to ensure optimal safe use of TISSEEL by spray application the following recommendations should be followed:

Recommended pressure, distance and devices for spray application of TISSEEL					
Surgery	Spray set to be used	Applicator tips to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open wound	Tisseel / Artiss Spray Set	n.a.	EASYSPRAY	10-15 cm	1.5-2.0 bar (21.5-28.5 psi)
	Tisseel / Artiss Spray Set 10 pack	n.a.	EASYSPRAY		
Laparoscopic/ minimally invasive procedures	n.a.	DUPLOSPRAY MIS Applicator 20cm	DUPLOSPRAY MIS Regulator	2-5 cm	1.2-1.5 bar (18-22 psi)
			DUPLOSPRAY MIS Regulator NIST B11		
		DUPLOSPRAY MIS Applicator 30cm	DUPLOSPRAY MIS Regulator		
			DUPLOSPRAY MIS Regulator NIST B11		
		DUPLOSPRAY MIS Applicator 40cm	DUPLOSPRAY MIS Regulator		
			DUPLOSPRAY MIS Regulator NIST B11		
		Replaceable tip	DUPLOSPRAY MIS Regulator		
			DUPLOSPRAY MIS Regulator NIST B11		

When spraying the TISSEEL, changes in blood pressure, pulse, oxygen saturation, and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

For the application of TISSEEL in enclosed thoracic and abdominal spaces the DUPLOSPRAY MIS applicator and regulator system is recommended. Please refer to the instruction manual of the DUPLOSPRAY MIS device.

For posology, incompatibilities, and interactions, please refer to the full SPC.
Medicinal product subject to medical prescription.
In some countries TISSEEL Fibrin Sealant is licensed under the trademark TISSUCOL Fibrin Sealant.

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