



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Fibrin sealant/adhesive/ haemostatic agent

Proprietary Product Name: Tisseel VH/SD

Sponsor: Baxter Healthcare Pty Ltd

**May 2012**

**TGA** Health Safety  
Regulation

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# I. Introduction to Product Submission

## Submission Details

<i>Type of Submission:</i>	Extension of Indications, Additional Method of Administration
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	25 January 2012
<i>Active ingredient(s):</i>	Fibrin sealant/adhesive/haemostatic agent
<i>Product Name(s):</i>	Tisseel VH/SD
<i>sponsor's Name and Address:</i>	Baxter Healthcare Pty Ltd 1 Baxter Drive Toongabbie NSW 2146
<i>Dose form(s):</i>	Two deep frozen solutions
<i>Strength(s):</i>	2 mL, 4 mL and 10 mL
<i>Container(s):</i>	Both Sealer Protein Solution and Thrombin Solution are contained in two separate chambers of a single use double chamber syringe made of polypropylene.
<i>Pack size(s):</i>	1 mL, 2 mL and 5 mL of each solution.
<i>Approved Therapeutic use:</i>	For mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks.
<i>Route(s) of administration:</i>	Topical
<i>Dosage:</i>	The required dose depends upon the size of the surface to be covered. See Product Information (PI) for recommendations.
<i>ARTG Number (s)</i>	147141

## Product Background

Tisseel VH/SD is a fibrin sealant product. It is a mixture of human plasma derived coagulation factors, which when mixed together result in the formation of a solid fibrin clot. It is currently registered for the following indications:

- as an adjunct to haemostasis during surgical procedures when control of bleeding by conventional surgical techniques is ineffective or impractical;
- as a sealant as an adjunct for closure of colostomies; and
- as a sealant and/or adhesive for use in autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI).

Registration for the last indication was approved in March 2010.<sup>1</sup>

The product is presented as two separate solutions which are mixed at the site of application by means of a double syringe device. The active ingredients in the currently registered formulation are as follows:

<sup>1</sup> TGA. AusPAR for fibrin sealant (Tisseel VH/SD), March 2010. Available from: <http://www.tga.gov.au/pdf/auspar/auspar-tisseel-vhsd.pdf>

### 1. "Sealer Protein Solution"

- Fibrinogen (human) 72 – 110 mg per mL Coagulation factor
- Factor XIII (human) 1.2 – 10 IU per mL Coagulation factor
- Aprotinin (synthetic) 3000 KIU per mL Fibrinolysis inhibitor

### 2. "Thrombin Solution"

- Thrombin (human) 500 IU per mL Coagulation factor
- Calcium chloride 40 mmol per mL Clotting activator

The sponsor also markets another fibrin sealant/adhesive product under the tradename 'Artiss'. This product contains a reduced concentration of thrombin and is currently only approved to assist in the adherence of autologous skin grafts in burns patients.

This AusPAR describes the evaluation of an application from Baxter Healthcare Pty Ltd (the sponsor) which sought approval for a new indication (to fix surgical mesh during hernia repair). The application also sought approval for an additional method of administration; using a spray device. The spray method of administration has been approved for the Artiss product.

The sponsor noted that abdominal wall hernia repair is one of the most common general surgical procedures undertaken. In Australian public hospitals in 2007 - 2008, there were 37,254 patient admissions for abdominal wall hernia repair (Australian Hospital Statistics <http://www.aihw.gov.au>). The large majority of the admissions were for inguinal hernias (followed by umbilical hernias and ventral or incisional hernias). Traditionally, inguinal hernias have been repaired using open surgical procedures. Recently, the availability of prosthetic meshes has led to tension free methods (the most common being the Lichtenstein technique) of reinforcing the inguinal region. In addition, laparoscopic inguinal hernia repair techniques (the two most common are transabdominal preperitoneal [TAPP] repair and totally extraperitoneal [TEP] repair) are increasing in popularity.

Regardless of the surgical technique, the prosthetic mesh used during abdominal wall hernia repair needs to be secured in place. The traditional methods for securing the mesh have been sutures, staples or tacks. However, these methods may cause trauma to the underlying visceral tissues and nerves resulting in pain and/or numbness. The use of a fibrin sealant, such as Tisseel, to secure the mesh would avoid the unnecessary trauma associated with the traditional methods of mesh fixation.

A formal clinical development program has not been undertaken to support the use of Tisseel as a mesh sealant during hernia repair. Therefore, a literature based submission has been prepared to support this extension of indication for Tisseel. The submission did include one controlled clinical study Final Study Report.

## Regulatory Status

Tisseel was initially registered in Australia in 2002.

The original dosage form of Tissucol/Tisseel was first approved for use in Germany in November 1991 and is currently nationally licensed in 25 countries worldwide. Second and subsequent generations have also obtained widespread licensing. The current generation Fibrin Sealant VH S/D (proposed for use in this indication) was first licensed in July 2006 in the USA and is currently licensed in 25 countries worldwide.

The sponsor stated that Tisseel received marketing authorisation for the indication of mesh fixation in hernia repair in the United Kingdom in 2010.

### **Product Information**

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## **II. Quality Findings**

### **Quality Summary and Conclusions**

There was no requirement for a quality evaluation in a submission of this type.

## **III. Nonclinical Findings**

### **Introduction**

The sponsor applied to extend the indications for Tisseel VH S/D to include mesh fixation in hernia repair as an alternative or adjunct to sutures or staples. The proposed indication does not distinguish between different types of hernia.

The sponsor submitted a well conducted literature based submission, with references clearly identified as pivotal, supportive or clinical. Because of the ongoing nature of this research field, a few relevant papers published subsequent to the literature review have been identified and considered by the nonclinical evaluator as part of this evaluation report.

### **Pharmacology**

#### **Primary pharmacodynamics**

In support of the proposed indication, the efficacy or biocompatibility of fibrin sealants was examined in *in vitro* studies and in rat and pig models of hernia. Most of the studies used Tisseel products (including Tissucol) which, although not identical to the current Tisseel VH S/D, were earlier generations of the same product and may be considered acceptable. A comparison of Artiss and Tisseel in an *in vitro* study (Jenkins *et al*, 2010) demonstrated a difference in the strength of fixation with different formulations, with the product with the higher thrombin concentration (500 IU/mL, Tisseel) forming lower strength joins than the product with less thrombin (4 IU/mL, Artiss).<sup>2</sup> Therefore, findings with Tisseel/TISSUCOL may not always be predictive for other fibrin sealants (Tredree *et al.*, 2006).<sup>3</sup>

#### ***Efficacy in inguinal hernia repair***

To fix this type of hernia the mesh is extra-peritoneal and is fixed to muscle. The available nonclinical evidence indicates that fibrin sealant would be an effective alternative to sutures or staples in the mesh repair of inguinal hernia. *In vitro* studies have shown that fixation of a mesh to muscle was stronger with fibrin sealant than by interrupted sutures (Schwab *et al*, 2007) and a variety of mesh types protruded less through a defect in the

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<sup>2</sup> Jenkins ED, Melman L, Frisella MM, Deeken CR, Matthews BD. Evaluation of acute fixation strength of absorbable and nonabsorbable barrier coated mesh secured with fibrin sealant. *Hernia* 2010; 14:505-509.

<sup>3</sup> Tredree RW, Beierlein I, Debrix A et al. Evaluating the differences between fibrin sealants: recommendations from an international advisory panel of hospital pharmacists. *Eur J Hosp Pharm Sci* 2006; 12: 3-9.

muscle when fibrin sealant was used instead of sutures (Schwab *et al*, 2008).<sup>4,5</sup> However, it should be noted that the force withstood *in vitro* when a mesh was bound to muscle using fibrin sealant varied considerably with the mesh type used (Schug Pass *et al*, 2010b).<sup>6</sup> Meshes have been successfully fixed using fibrin sealant into the inguinal region of pigs, with no mesh shrinkage or migration (Olmi *et al*, 2007).<sup>7</sup> A comparison of the use of staples with fibrin sealant to fix meshes in the groins of pigs showed similar fixation strengths between the fibrin sealant and Staple groups but smooth undistorted homogenous graft incorporation in the fibrin sealant group compared to clearly differentiated grafts in the stapled group (Katkhouda *et al*, 2001).<sup>8</sup> In a rat study, fibrin sealant appeared to be no better than no fixation after five days and much weaker than when staples were used (Hollinsky *et al*, 2009).<sup>9</sup> However, this study used a very thick layer of fibrin sealant, contrary to clinical use guidelines, and it was suggested that by 5 days the fibrin sealant had not completely disintegrated (Fortelny and Glaser, 2009).<sup>10</sup> Therefore these findings are unlikely to be clinically relevant provided the recommended thickness of Tisseel is used.

### ***Efficacy in preperitoneal hernia repair***

Preperitoneal hernia repair involves adhesion of the mesh to muscle. The nonclinical evidence supports the use of fibrin sealant as an alternative to sutures or staples when fixation is to muscle. In a rat model of ventral hernia using an onlay technique (in which fibrin sealant was used to adhere mesh to the muscle) all meshes passed the mechanical tests and there was no inflammation, whereas inflammation occurred around the staples in two rats in the staple-fixation group (Petter-Puchner *et al*, 2005).<sup>11</sup> In rats, when fibrin sealant was used to stick meshes to muscle, the bond was as strong in traction and pressure tests as when sutures were used, and mesh integration and vessel neo-formation were better for the fibrin sealant group (Suarez-Grau *et al*, 2009).<sup>12</sup>

### ***Efficacy in intraperitoneal/laparoscopic ventral hernia repair***

In contrast to the two previous hernia repair techniques, in which mesh fixation is to muscle, intraperitoneal approaches involve fixation of the mesh to an intact peritoneum. An *in vitro* comparison was made between the strength of the attachment of the

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<sup>4</sup> Schwab R, Schumacher O, Junge K *et al*. Fibrin sealant for mesh fixation in Lichtenstein repair: biomechanical analysis of different techniques. *Hernia* 2007; 11: 139-145.

<sup>5</sup> Schwab R, Schumacher O, Junge K *et al*. Biomechanical analyses of mesh fixation in TAPP and TEP hernia repair. *Surgical Endoscopy* 2008; 22: 731-738.

<sup>6</sup> Schug-Pass C, Lippert H, Köckerling F. Mesh fixation with fibrin glue (Tissucol/Tisseel®) in hernia repair dependent on the mesh structure-is there an optimum fibrin-mesh combination?-Investigations on a biomechanical model. *Langenbecks Arch Surg* 2010; 395: 569-574.

<sup>7</sup> Olmi S, Addis A, Domeneghini C, Scaini A, Croce E. Experimental comparison of type of Tissucol dilution and composite mesh (Parietex) for laparoscopic repair of groin and abdominal hernia: observational study conducted in a university laboratory. *Hernia* 2007; 11: 211-215.

<sup>8</sup> Katkhouda N, Mavor E, Friedlaner MH *et al*. Use of fibrin sealant for prosthetic mesh fixation in laparoscopic extraperitoneal inguinal hernia repair. *Annals of Surgery* 2001; 233: 18-25.

<sup>9</sup> Hollinsky C, Kolbe T, Walter I *et al*. Comparison of a new self-gripping mesh with other fixation methods for laparoscopic hernia repair in a rat model. *J Am Coll Surg* 2009; 208: 1107-1114.

<sup>10</sup> Fortelny RH, Glaser KS. *J Am Coll Surg* 2009; 209: 543-544. Response to Hollinsky C, Kolbe T, Walter I, Joachim A, Sandberg S, Koch T and Thomas Rulicke T (2009) Comparison of a new self-gripping mesh with other fixation methods for laparoscopic hernia repair in a rat model.

<sup>11</sup> Petter-Puchner AH, Fortelny R, Mittermayr R, Öhlinger W, Redl H. Fibrin sealing versus stapling of hernia meshes in an onlay model in the rat. *Hernia* 2005; 9: 322-329.

<sup>12</sup> Suárez-Grau JM, Morales-Conde S, Martín-Cartes JA *et al*. Mesh fixation with sutures versus fibrin sealant in hernioplasty with reabsorbable prosthesis (polyglycolic acid and trimethylene carbonate). Experimental study in animals. *CIR ESP* 2009; 86: 242-248.

proprietary product TiMesh mesh to pig muscle compared to peritoneum using fibrin sealant. When the mesh was attached to muscle, the adhesion withstood a force greater than that expected to occur within an abdomen, whereas when the mesh was attached to peritoneum, the force withstood was about one third of that expected to occur within the abdomen (Schug-Pass *et al*, 2009).<sup>13</sup> As with fixation to muscle, fixation of a mesh with fibrin sealant to the peritoneum has been shown to be dependent on mesh type. *In vitro* studies using rabbit peritoneum demonstrated that two of seven different mesh types did not adhere to the peritoneum when fibrin sealant was used (Jenkins *et al*, 2010).<sup>2</sup>

In a rat model in which fibrin sealant fixation of mesh to the peritoneum was compared to no adhesive mechanism, the fibrin sealant was more effective than no adhesion method, with herniation being observed in all controls after 14 days (Zieren *et al*, 1999).<sup>14</sup> However, in pig models in which fixation to the peritoneum by fibrin sealant was compared to tacks, fibrin sealant resulted in greater mesh contraction and migration (Clarke *et al*, 2010), a greater likelihood of meshes folding (Erikson *et al*, 2008) and weaker fixation, although this difference was not statistically significant (Erikson *et al*, 2008).<sup>15,16</sup> When TiMesh was implanted into six different pigs, with fibrin sealant alone being used to fix the mesh to the peritoneum, 50% of the meshes were unreliably fixed, with one completely dislocated (Schug-Pass *et al*, 2009). Thus, both *in vitro* and *in vivo* data provide limited support for the efficacy of fibrin sealant being used as an alternative to sutures or staples in the fixation of mesh to the peritoneum for hernia repair. However, some evidence was provided to support the use of Tisseel as an adjunct to staples, tacks or sutures in this type of hernia repair.

Three studies in the rat demonstrated that fewer adhesions formed when fibrin sealant was used in combination with sutures; two of these involved a patch (Evrard *et al*, 1996 and Toosie *et al*, 2000) and one simply closed the excision with sutures (Lindenberg *et al*, 1985).<sup>17,18,19</sup> Less adhesion was also demonstrated when fibrin sealant was used with tacks in a pig model (Martín-Cartes *et al*, 2008).<sup>20</sup> In a study in rats half of the cPTFE meshes were dislocated when only sutures were used, whereas there was no mesh

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<sup>13</sup> Schug-Pass C, Lippert H, Köckerling F. Fixation of mesh to the peritoneum using a fibrin glue: investigations with a biomechanical model and an experimental laparoscopic porcine model. *Surg Endosc* 2009; 23: 2809-2815.

<sup>14</sup> Zieren J, Castenholz E, Baumgart E, Müller JM. Effects of fibrin glue and growth factors released from platelets of abdominal hernia repair with a resorbable PGA mesh: experimental study. *J Surg Res* 1999; 85: 267-72.

<sup>15</sup> Clarke T, Katkhouda N, Mason RJ et al. Fibrin glue for intraperitoneal laparoscopic mesh fixation: a comparative study in a swine model. *Surg Endosc* 2010.

<sup>16</sup> Erikson JR, Bech JI, Linnemann D, Rosenberg J. Laparoscopic intraperitoneal mesh fixation with fibrin sealant (Tisseel®) vs. Titanium tacks: a randomised controlled experimental study in pigs. *Hernia* 2008; 12: 483-491.

<sup>17</sup> Evrard VA, de Bellis A, Boeckx W, Brosens IA. Peritoneal healing after fibrin glue application: a comparative study in a rat model. *Human Reproduction* 1996; 11: 1877-1880.

<sup>18</sup> Toosie K, Gallego K, Stabile BE, Schaber B, French S, de Virgilio C. Fibrin glue reduces intra-abdominal adhesions to synthetic mesh in a rat ventral hernia model. *American Surgeon* 2000; 66: 41-45.

<sup>19</sup> Lindenberg S, Steentoft P, Sorensen S, Olesen HP. Studies on prevention of intra-abdominal adhesion formation by fibrin sealant. An experimental study in rats. *Acta Chirurgica Scandinavica* 1985; 151: 525-527.

<sup>20</sup> Martín-Cartes JA, Morales-Conde S, Suárez-Grau JM et al. Role of fibrin glue in the prevention of peritoneal adhesions in ventral hernia repair. *Surg Today* 2008; 38: 135-140.



dislocation when sutures were used in combination with fibrin sealant; in addition, there were less severe adhesions in the fibrin sealant group (Petter-Puchner *et al*, 2008).<sup>21</sup>

### ***Efficacy in paraoesophageal hernia repair***

A rare type of hernia is the paraoesophageal hernia. A single nonclinical study in the pig investigated the use of fibrin sealant to fix a titanium coated polypropylene mesh round the oesophagus (Fortelny *et al*, 2010). In this study the meshes were not dislocated and good integration of the meshes occurred in all seven pigs. Thus, the limited nonclinical data support the use of fibrin sealant as an effective alternative to sutures or staples in the mesh repair of paraoesophageal hernia.<sup>22</sup>

### ***Conclusions regarding efficacy in animal models of hernia repair***

The data provided lend support for the use of Tisseel as an alternative to staples or sutures for mesh fixation in inguinal hernia repair and preperitoneal open ventral hernia repair, where fixation is primarily to muscle. In intraperitoneal approaches/laparoscopic ventral hernia repair techniques, where mesh needs to be fixed to an intact peritoneum, Tisseel alone may not be adequate and additional fixation using sutures and/or tacks may be necessary. In response to a question, the sponsor confirmed that further studies were required to investigate the potential use of Tisseel alone in laparoscopic ventral hernia repair but some evidence indicated Tisseel could be used in combination with sutures or staples/tacks. Therefore, the proposed indication, "*Mesh fixation in hernia repair, as an alternative or adjunct to sutures or staples*" may require further modification to indicate in which type of hernia repair it is acceptable to use Tisseel as an *alternative* to sutures or staples, and when it is more appropriate to use Tisseel as an *adjunct* to sutures or staples. Obviously, this requires further comment based on available clinical data but the animal data do not fully support the proposed broad indication. Differences in fixation strength were also noted with different mesh types, which may impact on clinical efficacy.

### **Secondary pharmacodynamics**

A number of published papers were submitted that investigated the use of fibrin sealant in animals to support indications other than mesh fixation in hernia repair. These papers have not been evaluated in regards to the indications that the authors were investigating. However, some of these papers provide useful information with respect to the general toxicity and local tolerance of fibrin sealant. These are discussed in the relevant sections of this report.

### **Pharmacokinetics**

No new nonclinical pharmacokinetic data for Tisseel VH S/D were provided with this submission. All the available evidence indicates that in animals the fibrin produced by fibrin sealants is dissolved *in vivo* within 7 days of application. The *in vivo* dissolution time is dependent on the thickness of the fibrin layer: a thick layer takes longer to dissolve than a thin layer.

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<sup>21</sup> Petter-Puchner AH, Wadler N, Redl H et al. Fibrin sealant (Tissucol) enhances tissue integration of condensed polytetrafluoroethylene meshes and reduces early adhesion formation in experimental intraabdominal peritoneal onlay mesh repair. *J Surgical Res* 2008; 150: 190-195.

<sup>22</sup> Fortelny RH, Petter-Puchner AH, Glaser KS et al. Fibrin sealant (Tisseel) for hiatal mesh fixation in an experimental model in pigs. *J Surgical Res* 2010; 162: 68-74.

## Toxicology

### General toxicity

There was no indication that fibrin sealant was cytotoxic. A number of different mammalian cell types (mesothelial, urothelial, myoblastic) and embryonal chick neuronal cells have been grown *in vitro* on fibrin matrices formed with fibrin sealant (Takazawa *et al*, 2005; Schoeller *et al*, 2004; Christman *et al*, 2004; Zeng *et al*, 1995).<sup>23,24,25,26</sup> All of these cell types grew equally well on fibrin matrices as on control media. In addition, mouse embryos have been grown *in vitro* on fibrin matrices formed with fibrin sealant, and again, fibrin had no detrimental effect (Rodrigues *et al*, 1988).<sup>27</sup>

Secondary pharmacodynamic studies have demonstrated that fibrin sealant is compatible with neuronal growth. In one rat study a comparison was made between fibrin sealant and sutures as methods of repairing dissected nerves (Maragh *et al*, 1990).<sup>28</sup> The axonal quality (measured by the onset and peak latency periods) of the repaired nerves appeared to be the same for the two repair methods. However, the quantity of axons (as measured by peak amplitude and conduction velocity) was less in the fibrin sealant group. Contact of fibrin sealant with nerves is not expected to result in toxicity.

The biocompatibility of fibrin sealant and inguinal adipose tissue was investigated in rats in the context of surgical autogenous fat grafts (Karaçal *et al*, 2007).<sup>29</sup> All fat grafts were successful, and no necrosis or liquefaction occurred. Indeed, the fat grafts survived better (had a larger volume) when fibrin sealant was used. Thus, contact of fibrin sealant with adipose tissue is not expected to result in toxicity.

The use of fibrin sealant in combination with prolene sutures was examined in a study to join a dissected aorta in pigs (Witter *et al*, 2010).<sup>30</sup> This was a long term (12 month) single dose study in which no adverse effects were observed in the fibrin sealant group; fibrin sealant was not toxic to vascular smooth muscle cells in the pig.

In conclusion, no cytotoxicity has been observed with fibrin sealant *in vitro* or *in vivo* with a variety of different cell types. In addition, unwanted adhesions often occurred at a lower frequency and sometimes a lower intensity after surgery in nonclinical studies when fibrin sealant was used.

### Genotoxicity, carcinogenicity and reproductive toxicity

Negative results were obtained in the bacterial reverse mutation studies (Ames tests) conducted on various components of Tisseel VH S/D (sealer protein solution containing

<sup>23</sup> Takazawa R, Yamato M, Kageyama Y, Okano T, Kihara K. Mesothelial cell sheets cultured on fibrin gel prevent adhesion formation in an intestinal hernia model. *Tissue Engineering* 2005; 11: 618-625.

<sup>24</sup> Schoeller T, Neumeister MW, Huemer GM et al. Capsule induction technique in a rat model for bladder wall replacement: an overview. *Biomaterials* 2004; 25: 1663-1673.

<sup>25</sup> Christman KL, Fok HH, Sievers RE, Fang Q, Lee RJ. Fibrin glue alone and skeletal myoblasts in a fibrin scaffold preserve cardiac function after myocardial infarction. *Tissue Engineering* 2004; 10: 403-409.

<sup>26</sup> Zeng L, Sigismund H, Redl H, Schlag G. Fibrin sealant matrix supports outgrowth of peripheral sensory axons. *Scand J Plast Reconstr Hand Surg* 1995; 29: 199-204.

<sup>27</sup> Rodrigues FA, van Rensburg JHJ, de Vries J, Sonnendecker EWW. The effect of fibrin sealant on mouse embryos. *J in vitro fertilization and embryo transfer* 1988; 5: 158-160.

<sup>28</sup> Maragh H, Meyer BS, Davenport D, Gould JD, Terzis JK. Morphofunctional evaluation of fibrin glue versus microsuture nerve repairs. *J Reconstructive Microsurgery* 1990; 6: 331-337.

<sup>29</sup> Karaçal N, Çobanoğlu Ü, Ambarcioğlu Ö, Kutlu N. The effect of fibrin glue on fat graft survival. *J Plast Reconstruct Aesthet Surg* 2007; 60: 300-303.

<sup>30</sup> Witter K, Tonar Z, Matejka VM et al. Tissue reaction to three different types of tissue glues in an experimental aorta dissection model: a quantitative approach. *Histochemistry Cell Biol* 2010; 133: 241-259.

bovine aprotinin; synthetic aprotinin; human thrombin solution). The standard battery of genotoxicity studies have not been conducted but this is generally not required for a biological product.

No studies for carcinogenicity or reproductive toxicity have been conducted but this is not considered a deficiency for this type of product.

### **Local Tolerance**

Histopathology was conducted in rats and pigs in primary pharmacodynamic studies and in rats, dogs and pigs in secondary pharmacodynamic studies. In all cases fibrin sealant was well tolerated locally. When signs of inflammation were observed, they were considered to be part of the healing process (Katkhouda N *et al*, 2001; Olmi *et al*, 2007; Witter *et al*, 2010).<sup>7,8,30</sup> The fibrin network dissolved within a week *in vivo* in nonclinical studies and therefore long term local tolerance issues are not expected.

### **Nonclinical Summary and Conclusions**

Nonclinical primary pharmacodynamic data have been generated *in vitro* and in rat and pig models of hernia. The use of fibrin sealant combined with sutures or staples resulted in less unwanted adhesion in the rat or pig, respectively.

The nonclinical data support the use of fibrin sealant as an alternative to sutures or staples for mesh fixation in inguinal hernia repair.

The nonclinical data indicate that fibrin sealant is less effective at binding mesh to peritoneum than to muscle. Thus, the nonclinical data do not support the use of fibrin sealant alone as a mesh fixation method when the mesh is being fixed to the peritoneum, such as in the underlay intraperitoneal technique for ventral hernia repair. Additional fixation using sutures and/or tacks may be necessary for this type of hernia repair.

A number of secondary pharmacology studies were submitted that provided information related to general toxicity and local tolerance.

The *in vivo* dissolution of fibrin produced by fibrin sealants is dependent on the thickness of the layer applied; dissolution was usually complete within 7 days in nonclinical studies.

No cytotoxicity has been observed with fibrin sealants in *in vitro* or *in vivo* studies that have investigated a variety of cell types.

No new genotoxicity, carcinogenicity or reproductive toxicity data were provided for this extension of indication.

Fibrin sealant was well tolerated locally in all evaluated nonclinical studies.

No additional toxicities were noted with the newly submitted data.

The nonclinical data do not support the proposed indication in its entirety. The proposed new indication for the fibrin sealant Tisseel VH S/D is: mesh fixation in hernia repair, as an alternative or adjunct to sutures or staples. The nonclinical data support the use of Tisseel VH S/D as an adjunct to sutures or staples. The data also support the use of Tisseel VH S/D as an alternative to sutures or staples for the adherence of mesh to muscle (such as occurs for inguinal hernia repair or the onlay extraperitoneal technique for mesh repair of ventral hernia). However, the nonclinical data do not support the use of Tisseel VH S/D as an alternative to sutures or staples for the adherence of mesh to the peritoneum (such as occurs with the underlay intraperitoneal technique for mesh repair of ventral hernia). Additional fixation methods would be required for this repair technique.

## IV. Clinical Findings

### Introduction

Tissucol/Tisseel was first licensed in 1991 and has undergone numerous dosage forms and strengths since this time. These variations have been based on thrombin concentration (4IU or 500IU), the source of thrombin (bovine or human), the method of viral inactivation (heat treated (HT), vapour heat treated (VH) or vapour heat and solvent/detergent treated (VH S/D)), the presence or absence of Factor XIII; and the presentation (deep frozen or lyophilised). The sponsor proposed using the most recent dosage form for mesh fixation in hernia repair (Tisseel VH S/D). This formulation is currently registered with the TGA.

The sponsor stated that a recent prospective, parallel design, randomised, double blind, multicentre clinical trial (n=278) comparing Tisseel VH to Tisseel VH S/D found that both viral inactivation treatment methods were bioequivalent with regards to the level of seroconversions caused by viral infection, with both treatment methods revealing a 0% incidence of B19 seroconversions one month after surgery.<sup>31</sup> The sponsor noted that additional nonclinical studies demonstrated that neither the omission of Factor XIII nor the implementation of a second virus inactivation step impaired the quality of the product in terms of efficacy, toxicity or tolerance.

The sponsor provided animal studies in order to demonstrate that Tisseel VH S/D (frozen and lyophilised), Fibrin Sealant VH (high FXIII) and Fibrin Sealant VH are statistically equivalent with regards to primary, secondary and sustained haemostasis and sealing. The sponsor stated that these three formulations were equally well tolerated in wound healing models, and that *in vitro* studies using human fibroblasts demonstrated excellent cellular compatibility and non-cytotoxicity.

Establishing bioequivalence between dosage forms of Tisseel is relevant, as it was unclear which dosage forms of Tisseel were used in the studies provided to the evaluators for assessing the safety and efficacy of Tisseel for mesh fixation during hernia repair.

The sponsor suggested the use of both lyophilised and deep frozen fast set (500 IU thrombin) Tissucol/Tisseel for use in mesh fixation during hernia repair, both of which were used in the unpublished pivotal study provided by the sponsor. Where reported, included studies used either lyophilised or deep frozen fast set Tissucol/Tisseel for mesh fixation in hernia repair, although specific thrombin concentrations were generally omitted. The sponsor stated that following Tisseel application, care must be taken to ensure that the mesh is held in place for the duration of the reaction (at least three to five minutes) to ensure correct mesh placement.

The sponsor did not undertake a formal clinical development program to support the request for additional indications for Tisseel. Instead, as Tisseel has an extensive registration history in Australia and overseas, the sponsor employed a hybrid literature based submission to support the application for the extension of indication. One unpublished pivotal study was provided and the remainder of the current Australian submission was comprised of published journal manuscripts. No pharmacology data (including pharmacokinetic analyses, pharmacology or dose finding studies) were submitted.

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<sup>31</sup> Lowe J, Luber J, Levitsky S et al, TISSEEL Clinical Study Group. Evaluation of the topical hemostatic efficacy and safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: a phase 3, randomized, double-blind clinical study. *J Cardiovasc Surg (Torino)* 2007; 48: 323-31.

The submission contained reports 15 efficacy studies, which were not subdivided into 'pivotal' or 'other' categories. Following a review of the material, the evaluators excluded three studies and included a further study. The evaluators classified five studies as 'pivotal studies' (one unpublished study provided by the sponsor and four published studies) and eight studies as 'other efficacy studies'. Also provided were three documents relating to postmarketing experience: two Periodic Safety Update Reports (PSURs) and one summary bridging report

The evaluators noted several shortcomings of the literature provided in the clinical submission. The sponsor did not clearly detail the population, intervention, comparator, outcome (PICO) of interest to this indication. Of particular concern was the fact that neither the comparators nor the safety and effectiveness outcomes were defined *a priori*. Therefore, the evaluators considered all mesh fixation methods to be valid comparators to Tisseel (including sutures, staples, tacks and glues other than Tisseel). Although one exclusion criterion was 'studies describing the use of a different fibrin sealant', the evaluators have assumed that this criterion was designed to ensure that at least one arm of any trial received Tisseel/Tissucol, rather than to exclude studies that compared Tisseel with a different fibrin sealant.

The evaluators noted that the selection (inclusion and exclusion) criteria applied to the search output were minimal, ostensibly to allow a broad range of studies to be eligible for inclusion. However, upon reviewing the search output, the evaluators identified an additional five eligible studies which the sponsor failed to include in the submission.<sup>32, 33, 34, 35, 36</sup> TGA guidance recommends that sponsors should demonstrate how *each* article identified by the search did or did not meet the selection criteria.<sup>37</sup>

The evaluators noted that the sponsor has not met this quality criterion. Instead, the sponsor provided an aggregated table which defined the exclusion categories and detailed the corresponding number of articles excluded, which does not permit comparison between the sponsor's and the evaluators' selection decisions.

The evaluators could not ascertain the sponsor's reasons for excluding these relevant studies and have therefore included and evaluated these studies as part of this evaluation. A further limitation of the selection criteria was that the sponsor did not mandate that, for case series, a minimum number of patients were enrolled, nor the need for these patients to be consecutively enrolled.

The sponsor provided a table of studies which were used to inform on the efficacy of Tisseel when used for mesh fixation in hernia repair. However, elsewhere in the submission, the sponsor provided a table of different studies which were used to inform on the efficacy of this product. Additionally, the sponsor did not clearly indicate which

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<sup>32</sup> Canonico S, Santoriello A, Campitiello et al. Mesh fixation with human fibrin glue (Tissucol) in open tension-free inguinal hernia repair: a preliminary report. *Hernia* 2005;9:330-33.

<sup>33</sup> Fortelny RH, Schwab R, Glaser KS et al. The assessment of quality of life in a trial on lightweight mesh fixation with fibrin sealant in transabdominal preperitoneal hernia repair. *Hernia* 2008;12:499-505.

<sup>34</sup> Olmi S, Scaini A, Erba L, Croce E. Use of fibrin glue (Tissucol) in laparoscopic repair of abdominal wall defects: preliminary experience. *Surg Endosc* 2007; 21: 409-13.

<sup>35</sup> Olmi S, Scaini A, Erba L, Bertolini A, Croce E. Laparoscopic repair of inguinal hernias using an intraperitoneal onlay mesh technique and a Parietex composite mesh fixed with fibrin glue (Tissucol). Personal technique and preliminary results. *Surg Endosc* 2007; 21: 1961-4.

<sup>36</sup> Schmidt SC, Langrehr JM. Autologous fibrin sealant (Vivostat®) for mesh fixation in laparoscopic transabdominal preperitoneal hernia repair. *Endoscopy* 2006; 38: 841-4.

<sup>37</sup> TGA, *Literature-based submissions: points to consider*, Therapeutic Goods Administration, Canberra, 2003; available at <http://www.tga.gov.au/pdf/pm-literature-based-submissions.pdf>.

studies were considered pivotal or 'other' efficacy studies. The evaluators have therefore assumed that the sponsor considered all efficacy studies to be pivotal.

The evaluators have therefore compiled a table which presents an amalgamation of these studies (Table 1). Following an in depth analysis of the provided literature, the evaluators excluded four of the sponsor's efficacy studies and identified an additional efficacy study from the search output.<sup>36</sup> The evaluators then assigned a classification (pivotal or 'other') to reflect the quality of evidence and reporting presented. Justification for exclusion and classification of the efficacy studies provided by the sponsor is presented in Table 1 and in the comment below.

The sponsor presented four studies which the evaluators felt should have been excluded. One study reported upon the use of two different glues (Tisseel and N-butyl 2-cyanoacrylate), but did not report safety and efficacy outcomes separately for each patient group.<sup>38</sup> As the combined data could not be de-aggregated, the evaluators considered that the study was inappropriate for inclusion in the submission. Two studies did not explicitly state that Tisseel was used to affix the mesh during hernia repair.<sup>39, 40</sup> Rather, it appeared that Tisseel was used for wound sealing and hence these studies did not meet the sponsor's own inclusion criteria. The fourth study was a Cochrane systematic review which considered the use of fibrin sealant in a variety of surgical procedures.<sup>41</sup> Only the data on its use in mesh fixation in hernia repair were relevant for inclusion in this submission; however, these data were sourced from an RCT [randomised controlled trial] which was already identified as ineligible for inclusion in this submission.<sup>40</sup> Hence, inclusion of this systematic review was redundant.

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<sup>38</sup> Agresta F, Baldazzi GA, Ciardo LF et al. Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone 25) for TAPP inguinal hernia repair: initial experience. *Surg Laparosc Endosc Percutan Techn* 2007; 17: 91-4.

<sup>39</sup> Canonico S, Sciaudone G, Pacifico F, Santoriello A. Inguinal hernia repair in patients with coagulation problems: Prevention of postoperative bleeding with human fibrin glue. *Surgery* 1999; 125: 315-7.

<sup>40</sup> Fernández Lobato R, García Septiem J, Ortega Deballon P, Martín Lucas FJ, Ruíz de Adana JC, Limones Esteban M. Tissucol application in dermolipectomy and incisional hernia repair. *Int Surg* 2001; 86: 240-5.

<sup>41</sup> Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2003;(2):CD004171.

**Table 1: Efficacy studies presented by the sponsor. Table continued across two pages.**

<b>Efficacy studies presented by the sponsor</b>	<b>Evaluators' assessment (pivotal, other or excluded)</b>
Benfatto et al (2006) <sup>42</sup>	Other – although a level II study, no randomisation, blinding or allocation concealment were reported. Additionally, 25% of patients were lost to follow up with no reasons provided.
Benizri et al (2006) <sup>43</sup>	Other - historical control study (III-3)
Campanelli (2009) <sup>44</sup>	Pivotal
Canonico et al (1999) <sup>39</sup>	Excluded – did not explicitly state that Tisseel was used for mesh adhesion (appeared to be for wound healing)
Canonico et al (2007) <sup>45</sup>	Excluded – non-comparative case series
Carless et al (2003) <sup>41</sup>	Excluded – duplicate reporting of Lobato et al (2001)
Ceccarelli et al (2008) <sup>46</sup>	Other - retrospective case-control study (III-2)
Hidalgo et al (2005) <sup>47</sup>	Pivotal
Lau (2005) <sup>48</sup>	Pivotal
Lobato et al (2001) <sup>40</sup>	Excluded - did not explicitly state that Tisseel was used for mesh adhesion (appeared to be for subcutaneous tissue and muscle layer adhesion)
Lovisetto et al (2007) <sup>49</sup>	Pivotal
Novik et al (2006) <sup>50</sup>	Other - comparative study with concurrent controls (III-2)
Olmi et al (2007a) <sup>51</sup>	Pivotal

<sup>42</sup> Benfatto G, Benfatto SM, Strazzanti A et al. Fibrin glue in tension-free hernioplasty: our experience. *G Chir* 2006; 27: 392-4.

<sup>43</sup> Benizri EI, Rahili A, Avallone S, Balestro JC, Cai J, Benchimol D. Open inguinal hernia repair by plug and patch: the value of fibrin sealant fixation. *Hernia* 2006; 10: 389-94.

<sup>44</sup> Campanelli G, 'T.I.M.E.LI study', 2009, unpublished study submitted to the Therapeutic Goods Administration by the sponsor.

<sup>45</sup> Canonico S, Benevento R, Della Corte A, Fattopace A, Canonico R. Sutureless tension-free hernia repair with human fibrin glue (Tissucol) in soccer players with chronic inguinal pain: initial experience. *Int J Sports Med* 2007; 28: 873-6.

<sup>46</sup> Ceccarelli G, Casciola L, Pisanelli MC et al. Comparing fibrin sealant with staples for mesh fixation in laparoscopic transabdominal hernia repair: a case control-study. *Surg Endosc* 2008; 22: 668-73.

<sup>47</sup> Hidalgo M, Castillo MJ, Eymar JL, Hidalgo A. Lichtenstein inguinal hernioplasty: sutures versus glue. *Hernia* 2005;9:242-4.

<sup>48</sup> Lau H. Fibrin sealant versus mechanical stapling for mesh fixation during endoscopic extraperitoneal inguinal hernioplasty: a randomized prospective trial. *Ann Surg* 2005; 242: 670-5.

<sup>49</sup> Lovisetto F, Zonta S, Rota E et al. Use of human fibrin glue (Tissucol) versus staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty: a prospective, randomized study. *Ann Surg* 2007; 245: 222-31.

<sup>50</sup> Novik B, Hagedorn S, Mörk UB, Dahlin K, Skullman S, Dalenbäck J. Fibrin glue for securing the mesh in laparoscopic totally extraperitoneal inguinal hernia repair: a study with a 40-month prospective follow up period. *Surg Endosc* 2006; 20: 462-7.

<sup>51</sup> Olmi S, Scaini A, Erba L, Guaglio M, Croce E. Quantification of pain in laparoscopic transabdominal preperitoneal (TAPP) inguinal hernioplasty identifies marked differences between prosthesis fixation systems. *Surgery* 2007a; 142: 40-6.

<b>Efficacy studies presented by the sponsor</b>	<b>Evaluators' assessment (pivotal, other or excluded)</b>
Santoro et al (2007) <sup>52</sup>	Other - historical control study (III-3)
Schwab et al (2006) <sup>53</sup>	Other - retrospective comparative study (III-2)
Topart et al (2005) <sup>54</sup>	Other - historical control study (III-3)

The sponsor also provided two tables of studies which were used to inform on the safety of Tisseel when used for mesh fixation in hernia. The evaluators therefore compiled a table which presents an amalgamation of these studies (Table 2). Following an in depth analysis of the provided literature, the evaluators excluded four of these safety studies, included an additional seven efficacy studies which also reported safety outcomes<sup>42, 43, 46, 47, 51, 50, 54</sup>, and identified five additional eligible safety studies from the search output.<sup>32, 33, 34, 35, 36</sup>

The evaluators noted that the sponsor did not provide inclusion/exclusion criteria to justify the selection of safety studies and hence could not assess the sponsor's reasons for excluding many efficacy studies that also provided safety data. The evaluators considered that comparative safety data may be more informative than case series safety data and therefore included and evaluated the eight studies detailed above. Additionally, the evaluators could not assess the sponsor's reasons for excluding the five studies identified from the search output.<sup>32, 33, 34, 35, 36</sup>

**Table 2: Safety studies presented by the sponsor**

<b>Safety studies presented by the sponsor</b>	<b>Evaluators' assessment (included or excluded)</b>
Agresta et al (2007) <sup>38</sup>	Excluded – safety data not reported separately for each treatment group
Agresta and Bedin (2008) <sup>55</sup>	Included
Campanelli (2009) <sup>44</sup>	Included
Canonico et al (2007) <sup>45</sup>	Included
Canziani et al (2009) <sup>56</sup>	Included
Carless et al (2003) <sup>41</sup>	Excluded - duplicate reporting of Lobato et al (2001)
Descottes and Bagot d'Arc (2009) <sup>57</sup>	Included

<sup>52</sup> Santoro E, Agresta F, Buscaglia F, Mulieri G, Mazzarolo G, Bedin N, Mulieri M. Preliminary experience using fibrin glue for mesh fixation in 250 patients undergoing minilaparoscopic transabdominal preperitoneal hernia repair. *J Laparoendosc Adv Surg Tech A* 2007; 17: 12-5.

<sup>53</sup> Schwab R, Willms A, Kröger A, Becker HP. Less chronic pain following mesh fixation using a fibrin sealant in TEP inguinal hernia repair. *Hernia* 2006; 10: 272-7.

<sup>54</sup> Topart P, Vandenbroucke F, Lozac'h P. Tisseel vs tack staples as mesh fixation in totally extraperitoneal laparoscopic repair of groin hernias: a retrospective analysis. *Surg Endosc* 2005;19:724-7.

<sup>55</sup> Agresta F, Bedin N. Transabdominal laparoscopic inguinal hernia repair: is there a place for biological mesh? *Hernia* 2008; 2: 609-12.

<sup>56</sup> Canziani M, Frattini F, Cavalli M, Agrusti S, Somalvico F, Campanelli G. Sutureless mesh fibrin glue incisional hernia repair. *Hernia* 2009; 13: 625-9.



<b>Safety studies presented by the sponsor</b>	<b>Evaluators' assessment (included or excluded)</b>
Fine (2006) <sup>58</sup>	Included
Lamm et al (2007) <sup>59</sup>	Excluded – Tisseel was used in cardiac surgery, not for mesh fixation in hernia repair
Lau (2005) <sup>48</sup>	Included
Lobato et al (2001) <sup>40</sup>	Excluded - did not explicitly state that Tisseel was used for mesh fixation (appeared to be for subcutaneous tissue and muscle layer adhesion)
Lovisetto et al (2007) <sup>49</sup>	Included
Santoro et al (2007) <sup>52</sup>	Included
Schwab et al (2006) <sup>53</sup>	Included

The 12 additional eligible safety studies, which were omitted by the sponsor, are shown in Table 3. These were included and evaluated by the clinical evaluators.

**Table 3: Additional safety studies identified and included by the clinical evaluators**

<b>Study details</b>	<b>Evidence type</b>
Hidalgo et al (2005) <sup>47</sup>	Comparative (pivotal efficacy study)
Olmi et al (2007a) <sup>51</sup>	Comparative (pivotal efficacy study)
Benfatto et al (2006) <sup>42</sup>	Comparative ('other' efficacy study)
Benizri et al (2006) <sup>43</sup>	Comparative ('other' efficacy study)
Ceccarelli et al (2008) <sup>46</sup>	Comparative ('other' efficacy study)
Novik et al (2006) <sup>50</sup>	Comparative ('other' efficacy study)
Schmidt and Langrehr (2006) <sup>36</sup>	Comparative ('other' efficacy study)
Topart et al (2005) <sup>54</sup>	Comparative ('other' efficacy study)
Canonico et al (2005) <sup>32</sup>	Case series, identified from search output
Fortelny et al (2008) <sup>33</sup>	Case series, identified from search output
Olmi et al (2007b) <sup>34</sup>	Case series, identified from search output
Olmi et al (2007c) <sup>35</sup>	Case series, identified from search output

A summary table of all the studies which were included and assessed by the evaluators is provided as Table 4.

<sup>57</sup> Descottes B, Bagot d'Arc M. Fibrin sealant in inguinal hernioplasty: an observational multicentre study in 1,201 patients. *Hernia* 2009; 13: 505–10.

<sup>58</sup> Fine AP. Laparoscopic repair of inguinal hernia using Surgisis mesh and fibrin sealant. *JLS* 2006; 10: 461–5.

<sup>59</sup> Lamm P, Adelhard K, Juchem G et al. Fibrin glue in coronary artery bypass grafting operations: casting out the Devil with Beelzebub? *Eur J Cardiothorac Surg* 2007; 32: 567-72.

**Table 4: Included studies**

Study details	NHMRC level of evidence*	Included for efficacy	Included for safety
Agresta and Bedin (2008) <sup>55</sup>	IV	X	Ü
Benfatto et al (2006) <sup>42</sup>	II	Ü	Ü
Benizri et al (2006) <sup>43</sup>	III-3	Ü	Ü
Campanelli (2009) <sup>44</sup>	II	Ü	Ü
Canonico et al (2007) <sup>45</sup>	IV	X	Ü
Canonico et al (2005) <sup>32</sup>	IV	X	Ü
Canziani et al (2009) <sup>56</sup>	IV	X	Ü
Ceccarelli et al (2008) <sup>46</sup>	III-2	Ü	Ü
Descottes and Bagot d'Arc (2009) <sup>57</sup>	IV	X	Ü
Fine (2006) <sup>58</sup>	IV	X	Ü
Fortelny et al (2008) <sup>33</sup>	IV	X	Ü
Hidalgo et al (2005) <sup>47</sup>	III-1	Ü	Ü
Lau (2005) <sup>48</sup>	II	Ü	Ü
Lovisetto et al (2007) <sup>49</sup>	II	Ü	Ü
Novik et al (2006) <sup>50</sup>	III-3	Ü	Ü
Olmi et al (2007a) <sup>51</sup>	II	Ü	Ü
Olmi et al (2007b) <sup>34</sup>	IV	X	Ü
Olmi et al (2007c) <sup>35</sup>	IV	X	Ü
Santoro et al (2007) <sup>52</sup>	III-3	Ü	Ü
Schmidt and Langrehr (2006) <sup>36</sup>	III-3	Ü	Ü
Schwab et al (2006) <sup>53</sup>	III-3	Ü	Ü
Topart et al (2005) <sup>54</sup>	III-3	Ü	Ü

\*Source: National Health and Medical Research Council (NHMRC) 2009<sup>60</sup>

### Pharmacokinetics/ Pharmacodynamics

No clinical data were submitted. The sponsor stated that the product is intended to be applied topically for local haemostasis or sealing with little likelihood of absorption of the components.

### Efficacy

#### Introduction

Overall, evidence of the efficacy of Tisseel for mesh fixation during hernia repair was obtained from a total of 13 studies (Table 4). These consisted of the 12 studies identified

<sup>60</sup> National Health and Medical Research Council, *NHMRC levels of evidence and grades for recommendations for developers of guidelines*, National Health and Medical Research Council, Canberra, 2009; available at: [www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/evidence\\_statement\\_form.pdf](http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf).

through examining the output of the sponsor's search of the literature, and one additional unpublished pivotal study provided by the sponsor. The evaluators have classified these studies as pivotal or 'other' studies. All pivotal studies were of sufficiently high methodological quality (NHMRC level II or III-1) and reported on the primary effectiveness outcomes of hernia recurrence and chronic pain (Table 4). All 'other' studies were of lower methodological quality and/or contained poor reporting of effectiveness outcomes. The formulation of Tisseel used in the 13 studies was not specified.

The evaluators consider that the primary effectiveness outcomes for hernia repair are hernia recurrence and chronic pain. Expert clinical opinion advises that although early recurrence usually occurs within three to four months, longer term recurrence may occur many years later. The evaluators consider additional outcomes such as groin discomfort, numbness, length of hospital stay and the time taken to return to normal activities to be secondary measures of the effectiveness of hernia repair.

### **Dosage selection for the pivotal studies**

The authors of the unpublished pivotal efficacy study stated that for each procedure, a kit of 2 mL of Tissucol/Tisseel (4 mL of fibrin sealant) was applied.<sup>44</sup> The authors did not provide a justification for the use of this specific amount of fibrin glue. In the remaining four pivotal efficacy studies, 1–2 mL of Tissucol/Tisseel was used per hernia. None of these studies provided a rationale for the use of this amount of Tisseel.

### **Pivotal Efficacy Studies**

Overall, the evaluators classified five studies as pivotal efficacy studies.<sup>44, 47, 48, 49, 51</sup> The remaining eight studies were classified as 'other' studies.<sup>36, 42, 43, 46, 50, 52, 53, 54</sup>

#### ***Study 1: Campanelli (2009)<sup>44</sup>***

This was a prospective, double blinded randomised controlled trial. It evaluated safety and effectiveness outcomes in patients undergoing inguinal hernia repair by the Lichtenstein technique after mesh fixation with Tissucol/Tisseel fibrin sealant, compared with mesh fixation with sutures. An active comparator (sutures) was used. This was a multinational, multicentre study which was conducted across seven study centres (Italy, France, Spain, Germany, Belgium, UK and Denmark). Patients were enrolled between 30 January 2006 and 19 April 2007.

#### *Inclusion and exclusion criteria*

The study population included active males aged between 18 and 80 years with either an uncomplicated unilateral or bilateral primary hernia (provided that only one hernia is operated on during the 12 months of study follow up), who were eligible for elective inguinal hernia repair using the Lichtenstein technique.

This study cannot inform on the safety and effectiveness of Tisseel for mesh fixation in hernia repair in patients outside of these parameters, or in eligible patients with comorbidities detailed in the exclusion criteria.

#### *Study treatments*

A movie demonstrating the exact standard technique to be used was delivered to the investigators. In each instance, a qualified surgeon experienced in the Lichtenstein technique performed the procedure in either an inpatient or outpatient setting.

In patients with a direct hernia the posterior wall was repaired with one to two absorbable stitches for inversion, and the sac was also inverted with absorbable sutures.

The type of anaesthesia used varied according to the study centre and included local, regional and general anaesthesia. The authors noted that concomitant general and local

anaesthesia could be combined. The same kind of mesh was used in all patients. A macroporous, heavyweight polypropylene, flat mesh measuring 8 x 15 cm was used in all patients. Although a variety of mesh brands were available for use during the study, there was no significant between group difference for the mesh brand used.

In the intervention group the mesh was fixed using Tisseel. The authors noted that Tisseel was prepared as outlined in the protocol, which was not supplied to the evaluators.

Surgeons used a 2 mL kit of Tisseel which, when prepared, contained a total volume of 4 mL of fibrin sealant (2 mL clottable protein solution and 2 mL thrombin solution). The Duploject syringe kit was used and was equipped with the spray attachment. A small spot of 0.5 mL was applied drop wise on the pubic tubercle under the mesh, and pressure was then applied for at least 30 seconds. The authors stated that the remaining 1.5 mL of Tisseel was applied by spraying; however, this does constitute a total of 4 mL of fibrin sealant. As such, it is unclear whether patients received 2 mL or 4 mL of Tisseel. Tisseel was sprayed over the entire surface of the mesh using the spray system connected to propellant gas (compressed air or nitrogen) at a pressure of approximately 1.5–2 bar, 5–20 L/min, sterilised via a sterile filter. The Duploject Spray Set was used only in connection with the Tissomat Pressure Control Device, which appears to be consistent with recent FDA advice regarding spray application of fibrin sealant.<sup>61</sup> The minimum spraying distance was 10 cm.

Authors stated that the skin was closed according to usual standard and drains were not used, and that wound dressings were used according to local practice. It was unclear whether these processes applied to both groups, or just to Tisseel patients.

The comparator group received mesh fixation using sutures. A Prolene 2/0 running suture was used, starting 2 cm medial to the pubic tubercle along the inguinal ligament until the level of internal ring. Following this, one to two Vicryl 2/0 or 3/0 stitches were applied on the internal oblique. Vicryl sutures are absorbed within 56–70 days. Closure of the external fascia was performed with a Vicryl 2/0 or 3/0 running suture.

#### *Efficacy variables and outcomes*

The TGA-adopted EU guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products states that it is necessary to design clinical studies in which the appropriate endpoint is assessed for each therapeutic indication proposed.<sup>62</sup> The therapeutic indication is mesh fixation in hernia repair. This pivotal study has presented chronic pain, numbness and groin discomfort at 12 months as endpoints for mesh fixation for hernia repair.

The evaluators noted that expert clinical opinion indicates that chronic pain and hernia recurrence are primary efficacy variables and that numbness and groin discomfort are secondary efficacy variables. The evaluators have used this approach throughout this evaluation.

Chronic pain was defined as pain lasting more than three months, and was assessed at 6 months and 12 months postoperatively using the visual analog scale (VAS). The scale measured from 0 mm (no pain) to 100 mm (worst conceivable pain). The VAS score permitted classification of pain as mild (0–30 mm), moderate (31–60 mm) or severe (>60

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<sup>61</sup> FDA, *FDA safety notification: risk of air or gas embolism when using air- or gas- pressurized spray devices*, U.S. Food and Drug Administration, Silver Spring, 2009; available at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm218523.htm>.

<sup>62</sup> EMEA, Committee for Medicinal Products for Human Use (CHMP), 2004, Guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products (CPMP/BPWG/1089/00); available at <http://www.tga.gov.au/pdf/euguide/bpwg108900en.pdf>.

mm)). Chronic pain was measured by patient self assessment, and no clinician evaluations were conducted. The VAS is a well accepted tool for pain measurement.

The number of patients with recurrent hernia was assessed, with the presence of hernia recurrence confirmed by an independent, blinded surgeon through a medical examination. Additional examinations such as ultrasound or reoperation could also provide further confirmation.

The authors also presented several secondary efficacy outcomes. These included:

- *Numbness*, defined as paraesthesia in the respective part of the body
- *Groin discomfort*, defined as a less severe nociception. The authors noted that discomfort is often used to describe a non continuous sensation in the groin or upper thigh, without need for analgesics and expressed as 'I sometimes feel it when...'

These variables were assessed preoperatively and at 1 week, 1 month, 6 months and 12 months postoperatively using the VAS. Patients were required to notify the worst sensation they had experienced during the last period of evaluation.

- *Patient satisfaction*

The authors stated that this was measured by the question 'Would you like to have the same operation again?', with patients required to answer yes or no.

- *Quality of life (QoL) evaluation*

QoL was measured using the SF12 questionnaire (12-item short form health survey), which the authors stated is a validated instrument. The SF-12 questionnaire comprises questions to measure the following areas: vitality (1 item), physical functioning (2 items), general health (1 item), role physical (2 items), bodily pain (1 item), social functioning (1 item), role emotional (2 items) and mental health (2 items). QoL was assessed before the operation, at 1 month and 6 month visits and 1 year post surgery.

- *Length of hospital stay*

The length of hospital stay was assessed at the first postoperative visit, and any readmissions to hospital were documented.

- *Time to return to normal activities*

The time to return to normal daily activities was assessed by collecting the exact date at the 1 month, 6 month or 12 month follow up visit. Readmissions to hospital were documented. The time to return to normal activity was evaluated by the Kaplan-Meier method.

#### *Statistical considerations*

The sample size calculation considered 2 sided test,  $\alpha = 5\%$  and a power of 80%. Estimation of the required sample size was based on the prevalence of chronic pain, numbness or groin discomfort at Month 12. The authors assumed an overall prevalence of 25% (chronic pain 10%, numbness 10% and groin discomfort 15%) in the sutures group and 12.5% in the Tisseel group. Based on this assumption, the authors were required to enrol a total of 298 patients (149 per treatment group). Planning for a dropout rate of 10%, the authors sought to enrol a total of 328 patients (164 per treatment group).

The evaluators noted that importantly, the authors did not provide a citation for this assumption. A recent Cochrane review identified that the prevalence of chronic pain after

open repair for inguinal hernia may be between 16.12% and 23.41%.<sup>63</sup> Hence this pivotal study may not have been sufficiently powered.

Randomisation was performed electronically, within 24 hours prior to surgery.

The authors stated that the evaluators and patients were blinded for the whole study. The surgical team were required to maintain the patient's blinding by not telling the patient which mesh fixation method had been used. However, the authors did not provide any details on how this was enforced. Follow up evaluations were performed by an evaluator who was unaware of the treatment group, such as a surgeon or a study nurse who was not present during the operation.

A clinical research organisation was contracted to conduct the statistical analysis. Data were analysed according to:

- "intention-to-treat" (ITT): all randomised patients who underwent the selected surgical procedure. This was verified by the presence of the date of surgery at visit two (intraoperative and until discharge)
- "per protocol" (PP): all patients from the ITT population without major protocol deviation.

Additionally, psychometric validation of the SF-12 questionnaire was conducted in patients with an exploitable questionnaire (that is, there was less than 50% missing data). This was conducted in the cross sectional population (all included patients with an exploitable questionnaire at preoperative visit) and the longitudinal population (all included patients with an exploitable questionnaire at preoperative visit and at least one post-baseline exploitable questionnaire at 1, 6 or 12 months).

All tests were 2 sided with a significance level of 5%. For the percentage of patients with at least one disabling complication at 12 months, 95% confidence interval was calculated. All analyses were performed using Statistical Analysis System (SAS) software, version 8.2.

Quantitative variables were described according to their frequency, mean, standard deviation, standard deviation to the mean, median, first and third quartiles, minimum and maximum values, and missing data. Qualitative variables were described according to the frequency and percentage of each of the ways of answering. The authors noted that qualitative variables may also be described according to the missing data that will be integrated into the calculation of the percentage, although this was not expanded upon.

For the efficacy criteria and psychometric validation of the SF-12, the following models were used when comparing the two groups:

- binary outcome variable: mixed logistic regression model with centre as random factor (to take centre effect into consideration)
- quantitative outcome variable: mixed covariance analysis (parametric) or if the assumptions (normality and homogeneity of the variances) are not met, mixed covariance analysis performed on rank data (non parametric) with centre as random factor.

For the time to return to normal activities and the time to the first readmission to hospital, median and 95% confidence interval (CI) were estimated by the Kaplan-Meier method. For the changes in scores from SF-12 questionnaire, comparisons could be graphically

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<sup>63</sup> McCormack K, Scott NW, Go PM, Ross S, Grant AM, EU Hernia Trialists Collaboration. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst Rev* 2008;(4):CD001785.

performed using cumulative distribution curves. These curves represent the change in score on the x-axis and the cumulative percentage of patients on the y-axis.

The primary analysis was performed on the prevalence of at least one disabling complication (chronic pain, numbness or groin discomfort) 12 months after the operation. Analysis was performed on the ITT and PP populations per randomisation group and in total. Regarding missing data, the statistical plan noted that the last value carried forward (LVCF) method was used for analysis of disabling complications, and that no replacement would be performed for other missing data. The primary criteria were analysed as follows:

- at least one disabling complication at 6 months
- at least one disabling complication at 12 months (proportion and 95% CI)
- at least one disabling complication at 12 months using LVCF method (proportion and 95% CI)
- the number of patients with disabling complications at 12 months using the LVCF method was compared according to intraoperative nerve recognition and also according to intraoperative nerve damage.

The authors performed subgroup analysis on the primary efficacy outcome according to active and retired patients.

Regarding hernia recurrence, analysis constituted measuring the number of recurrences and time to recurrence.

Data assessed at this point depended on the initial question of whether the patient had a recurrence (yes or no). If yes, data pertaining to the type of mesh, type of recurrence, time to recurrence, treatment for the recurrence and time to surgery recurrence were compiled.

Analysis of the secondary criteria was performed on the ITT and PP populations per randomisation group and in total. Generally, the authors used a mixed logistic regression model with the study centre as the random factor, to take centre effect into consideration when comparing the two groups. The only secondary criterion which was analysed in this manner was patient satisfaction. The quality of life analysis did not use the mixed logistic regression model with the study centre as the random factor. For quality of life, the number of exploitable questionnaires, score and change from preoperative visit to the analysed visit (1, 6 or 12 months) were compared between groups using mixed covariance analysis (parametric). If the assumptions (normality and homogeneity of the variances) were not met, mixed covariance analysis was performed on rank data (non parametric) with score at preoperative visit as a fixed factor and centre as a random factor.

For safety, between group differences were analysed using mixed covariance analysis performed on rank data with centre as random factor. Additionally, the authors used a mixed logistic regression model, with the study centre as the random factor, to take centre effect into consideration when comparing the two groups for the following safety outcomes:

- the number of patients with at least one wound healing complication and the number of patients with each type of complication
- early postoperative pain (the number of patients with pain score >30 mm at 1 week and 1 month)
- mid postoperative pain at 6 months (the number of patients with pain score >30 mm)

- for patients with no disabling pain, the number of patients with pain score  $\leq 30$  mm at 1 month, 6 months and 12 months
- use of analgesic treatment: the number of patients with at least one analgesic treatment used during the postoperative period and during the entire study
- operative complications.

Several modifications were made to the prespecified statistical analysis plan:

- A class 'no pain' was added to the severity classes 'mild', 'moderate' and 'severe' for the analysis of VAS scores for pain, numbness and groin discomfort.
- A second type of classification for VAS scores for pain, numbness and groin discomfort was added to the analyses: 0–9, 10–30, 31–50, 51–60 and 61–100. Shift tables were performed using these classes to describe patient evolution.
- As only 23 patients received preoperative aspirin or heparin, no subgroup analysis was performed.
- As the level of patients' activity could be related to the subjective evaluation of pain, the authors decided to perform subgroup analysis on the primary criterion according to retired patients and to active patients.
- The prevalence of at least one disabling complication at endpoint was also analysed for patients with at least one nerve cut and for patients with nerves preserved.

The authors stated that the following analytical issues were not applicable: adjustments for covariates, handling of dropouts or missing data, interim analyses and data monitoring, multicentre studies, multiple comparison/multiplicity and use of an 'efficacy subset' of patients.

#### *Participant flow*

A total of 325 patients were enrolled by seven study centres. Six patients were not randomised due to medical reasons at the request of the investigator, serious protocol deviation (hernia type was size 3 medial hernia (M3) instead of size 2 medial hernia (M2) in one patient), informed consent withdrawal (one patient) or other reason (not provided in three patients). A total of 319 patients were enrolled in the study and were randomised to the Tisseel group (n=159) or the sutures group (n=160).

Six Tisseel patients and one suture patient presented with at least one major protocol deviation, and were excluded from the PP analyses.

One hundred and fifty nine patients were randomised to receive Tisseel and 160 patients were randomised to receive sutures. Three patients did not undergo surgery: one Tisseel patient was lost to follow up prior to surgery, one suture patient withdrew informed consent, and no reason was provided for the remaining suture patient. Additionally, one patient randomised to the Tisseel group received sutures in error. The ITT population was defined as all randomised patients who experienced the surgical procedure, which equated to 158 patients per treatment group.

A high percentage of screened patients proceeded to randomisation (319/325, 98.2%). A relatively low number of these patients were lost to follow up (five patients per group, 3.2% per group), although no reasons were provided. The five lost Tisseel patients were followed for mean 33.60 days (standard deviation [SD] 61.84) and the five lost sutures patients were followed for a mean 120.90 days (SD 89.15). Each group had five additional non completers. In the Tisseel group one patient died (0.63%, no further details given) and



four patients had serious protocol deviations. In the sutures group one patient withdrew informed consent (no further details given), two patients discontinued the study early due to hernia recurrence (1.25%), one patient discontinued due to 'other reasons' (no further data provided) and the remaining patient had a serious protocol deviation.

For the primary effectiveness variable (presence of at least one disabling complication) the length of follow up was 1 week and 1, 6 and 12 months post surgery. The secondary effectiveness variables and safety outcomes were also evaluated at these follow up periods. Safety outcomes were also measured intraoperatively.

#### *Baseline data*

Baseline data were provided for the ITT population (158 Tisseel patients and 158 sutures patients). The authors reported that there were no significant differences between the groups at baseline regarding weight, height, employment status or activity level.

The mean age of Tisseel patients and of sutures patients were  $55.23 \pm 14.08$  [range 19–84] years and  $56.11 \pm 13.32$  [range 21–80] years), respectively ( $p=0.657$ ). The mean body mass index (BMI) was approximately 25.5 for each treatment group. There were no significant between group differences regarding the side of the hernia (left or right).

Five suture patients and nine Tisseel patients presented with an American Society of Anesthesiology (ASA) score of III (patient with severe systemic disease that is not incapacitating), and the remaining patients presented with ASA scores I or II.

No information was provided regarding the duration of the hernias. Hernia severity was classified intraoperatively. A similar proportion of patients per treatment group presented with size 2 medial hernias (M2) (48/158 Tisseel patients and 47/160 suture patients). Although more sutures patients than Tisseel patients presented with size 2 lateral hernias (L2) (sutures 56/158, 35.4% versus Tisseel 47/158, 29.7%), this was not significant ( $p=0.694$ ). The authors reported that there were no significant between group differences for testicular location or volume; however, outcomes of any statistical analysis were not provided. Significantly more Tisseel patients (44/158) than sutures patients (29/158) were smokers ( $p=0.045$ ).

There were no significant between group differences for the remaining reported comorbidities (hypercholesterolaemia, hypertension, chronic obstructive pulmonary disease, constipation, symptomatic hyperplasia of the prostate and other pathologies). Additionally, there were no significant between group differences for platelet count or prothrombin level at baseline.

Enrolled patients were taking a variety of medications at the preoperative visit, most commonly for cardiovascular indications (39/158, 24.7% of Tisseel patients and 34/158, 21.5% of suture patients).

The severity of pain, numbness and groin discomfort was similar between groups at baseline. Mean preoperative pain (VAS) was approximately 21 points in both groups ( $p=0.981$ ). Most patients experienced pain at leisure or during exercise, rather than at rest (90.2% Tisseel and 92% sutures). Mean preoperative numbness was  $7.80 \pm 17.50$  in the Tisseel group and  $8.47 \pm 17.98$  in the sutures group. The ITT analysis found no significant between group differences for preoperative numbness ( $p=0.0736$ ). The majority of patients in each group reported no numbness at preoperative visit (71.52% of Tisseel patients and 69.6% of suture patients). Mean preoperative groin discomfort was  $22.72 \pm 23.72$  in the Tisseel group and  $23.35 \pm 23.03$  in the sutures group. The ITT analysis found no significant between group differences for preoperative groin discomfort ( $p=0.633$ ).

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### *Results for the primary efficacy outcome*

#### *Chronic pain*

Chronic pain is a clinically important outcome which may be a measure of the success of hernia repair. In the ITT analysis at six month follow up, no significant between group difference was seen for mean VAS score; however, the PP analysis found that the mean VAS score was significantly lower in Tisseel patients (6.34 (14.79)) than in suture patients (10.56 (18.12)) (p=0.0040). In the ITT analysis, pain was reported by significantly fewer sutures patients than Tisseel patients (26.5% versus 40.3%, p=0.0049). This trend was also noted in the PP analysis; however, no statistical analysis was provided.

In the ITT analysis, at 12 month follow up there was no significant between group difference for mean VAS score (Tisseel 3.87, suture 5.93) (p=0.1134). This finding was supported by the PP analysis for the same follow up period (Tisseel 3.92, suture 5.93) (p=0.1259).

In the ITT analysis, at 12 months there was no significant between group difference for the number of patients reporting 'no pain' (125/149 Tisseel patients and 115/150 suture patients (p=0.1104). This was supported by the PP analysis for the same follow up period (Tisseel patients 123/147 and suture patients 115/150) (no statistical analysis provided). The number of patients without pain was reported but considered redundant by the evaluators as it may be deduced from the chronic pain data.

#### *Recurrence*

The evaluators considered that the length of follow up in this study is too short to measure recurrence effectively.

Recurrence was only reported upon for the ITT population (159 Tisseel and 160 sutures patients). One Tisseel patient (0.63%) suffered a medial hernia (M2) recurrence at 176 days post surgery. Although the patient was not required to undergo further surgery, no details were provided on the resolution of the recurrence.

Two sutures patients (1.25%) suffered recurrence. One suffered a medial hernia (M2) recurrence at 107 days post surgery. This patient was not required to undergo further surgery, although no details were provided on the resolution of the recurrence. The second patient suffered a lateral hernia recurrence (L2) at 174 days post surgery. This patient required a further surgical procedure, and this occurred at 215 days.

Overall, the evaluators considered that the primary chronic pain and recurrence outcomes reported in this study were not supportive of Tisseel's superiority over sutures for mesh fixation in open, Lichtenstein inguinal hernia repair. However, these data did not indicate that Tisseel was significantly worse than sutures for this indication. No statements can be made about the overall effectiveness of Tisseel compared with sutures, due to the lack of reporting of the outcomes of any statistical analyses that may have been performed.

### *Results for other efficacy outcomes*

#### *Numbness*

No PP analyses were provided for this outcome. In the ITT analysis, mean numbness at 12 months was significantly lower in the Tisseel group (4.09 (10.60)) than in the Suture group (7.36 (14.6)) (p=0.0193). No significant between group differences were seen at any other time point.

In the ITT analysis, at 12 months 'no numbness' was reported by significantly more Tisseel patients (115/149, 77.2%) than suture patients (99/150, 66.0%) (p=0.0332). No significant between group differences were seen at any other time point.

### *Groin discomfort*

No PP analyses were provided for this outcome. In the ITT analysis, mean groin discomfort was significantly lower in Tisseel patients than suture patients at 1 week (Tisseel 20.89 (21.23) and suture 27.07 (25.32) ( $p=0.0076$ ), 1 month (Tisseel 11.86 (17.60) and suture 16.05 (19.47) ( $p=0.0449$ ) and 12 months (Tisseel 7.07 (14.58) and suture 10.21 (16.83)) ( $p=0.0491$ ). No significant between group differences were seen for the number of patients reporting 'no groin discomfort' at any time point.

### *Presence of at least one disabling complication*

No PP analyses were provided for this outcome. In the ITT analysis, no significant between group differences were noted at 1 week, 1 month, 6 month or 12 month follow up. The authors presented data for 'study endpoint' (6 or 12 month follow up), where significantly fewer Tisseel patients ( $n=12$ ) than suture patients ( $n=23$ ) reported at least one disabling complication ( $p=0.0344$ ).

The evaluators noted that the validity of this analysis is unclear as the authors used the 'last value carried forward' method to populate missing data. Further, the evaluators consider that time is an important factor in these outcomes, and the presentation of a composite analysis of various time points is inappropriate.

A subgroup analysis of this outcome was performed, according to patient activity level (active or retired). Of the 159 Tisseel patients, 106 were classified as active at baseline. Twelve month follow up data were available for 101/106 (95.3%). Of the 160 suture patients, 101 were classified as active at baseline. Twelve month follow up data were available for 95/101 (94.1%). At 12 months, the incidence of at least one disabling complication was significantly lower in active Tisseel patients (6/101, 5.9% (95% CI 2.2%–12.5%)) than in suture patients (12/95, 12.6% (95% CI 6.7%–21.0%)) ( $p=0.0407$ ).

A second subgroup analysis of this outcome was performed, according to whether or not at least one nerve was cut during the surgery.

The evaluators noted that the authors failed to provide a statistical analysis of any differences between the treatment groups. This shortcoming, coupled with the evaluators' concerns regarding the validity of the composite analysis, has led to the omission of the subgroup analysis data from this evaluation.

### *Patient satisfaction*

This outcome was evaluated according to each patient's answer to the following question: 'Would you like to have the same operation again? Yes/No.' The authors did not clearly define the time point at which this evaluation was conducted. A total of 154 patients per treatment group provided an answer to this question. Significantly more Tisseel patients (151, 98.1%) than suture patients (141, 91.6%) answered 'Yes' ( $p=0.0035$ ).

### *Quality of life*

There were several shortcomings of the SF-12 data reported in this study. A total of 286 (141 Tisseel and 145 suture) patients completed at least one SF-12 questionnaire, yet 39 of these questionnaires (13.6%) contained missing data. Additionally, a principal component analysis performed by the authors revealed that the psychometric properties of the mental health dimension were impaired.

Although suture patients reported declines for several dimensions at one month follow up, these were not significantly different to Tisseel scores. The authors reported that for the mean vitality dimension, suture patients reported a decline while Tisseel patients reported an improvement from preoperative baseline. This difference was claimed to be statistically significant ( $p=0.0195$ ).

The evaluators noted that it appears that the authors calculated this using data from patients who did not necessarily provide data for both baseline and one month follow up. The evaluators calculated the mean preoperative score and one month score in the 115 Tisseel patients and 113 suture patients who provided both of these values. Tisseel patients reported a mean 5.97 unit improvement (not mean 6.30 as reported) and suture patients reported a mean 2.63 unit decline (not 2.80 as reported). Hence, it is unclear whether the provided statistical analysis of the between group difference for mean vitality is valid.

Additionally, this noted improvement did not extend to either the 6 or 12 month follow up periods. The evaluators considered that immediate postoperative outcomes at one month are not reflective of long term patient outcomes, and hence the clinical significance of this between group difference is low.

No other between group differences was seen for any dimension at any time period. These outcomes are not supportive of Tisseel patients' reported satisfaction with the surgery.

#### *Length of hospital stay*

The authors did not provide any statistical analysis for this outcome. Data were reported for 156 Tisseel patients and 157 suture patients, and the median duration of hospital stay was 9 hours for both groups. For 30/156 Tisseel patients (19.2%) and 32/157 suture patients (20.4%), the postoperative hospital stay was  $\geq 24$  hours.

#### *Time to return to normal activities*

The median time for patients to return to normal activity was 14 days (95% CI 13–17) in the Tisseel group and 15 days (95% CI 14–16) in the Suture group. The authors did not provide any statistical analysis for this outcome.

#### *Operative time*

The mean operative time in the Tisseel and Suture groups were  $39.82 \pm 12.13$  minutes and  $41.06 \pm 11.89$  minutes, respectively (no statistical analysis provided).

Overall, the evaluators considered that the secondary outcomes reported for pain, numbness and groin discomfort were supportive of Tisseel's effectiveness in mesh fixation for hernia repair.

#### ***Study 2: Hidalgo et al (2005)<sup>47</sup>***

This was purportedly a prospective, randomised comparative study. However, all patients had bilateral hernias and sutures were used to affix the mesh on the right side and Tissucol to affix the mesh on the left side. Hence, the evaluators considered this study to be a pseudo randomised controlled trial (NHMRC level III-1).

The study aimed to assess whether fibrin glue could be used for mesh fixation in hernia repair and to compare the rates of hernia recurrence and postoperative pain in fibrin glue patients with suture patients. All surgeries were performed by the same surgeon between January 2001 and July 2003 at the 12 de Octubre University Hospital in Madrid, Spain.

#### *Inclusion and exclusion criteria*

Patients with bilateral inguinal hernia were included in the study. No exclusion criteria were reported.

#### *Study treatments*

Patients received antibiotic prophylaxis using a third generation cephalosporin (2 g before surgery and 1 g every 24 hours postoperatively for two days). Thirty four patients (61.8%) were given thromboembolic prophylaxis with low molecular weight heparin for 48 hours

after surgery. All surgeries were open procedures performed using the Lichtenstein technique under regional (epidural) anaesthesia.

All procedures utilised a polypropylene mesh of 15 x 7 cm in size, with sutures used for mesh fixation on the right side and fibrin glue on the left side of each patient. Patients in the Tissucol group were subdivided into two halves. Tissucol was applied to the first 23 patients by catheter application and to the second 23 patients by spraying.

The evaluators noted that this suggests there were 46 patients in the cohort instead of 55.

Two millilitres of Tissucol were used for each hernia. The authors did not state whether the mesh was held in place after the Tissucol was applied, to aid adhesion. For the Suture group, fixation of the mesh was achieved by single polypropylene 2/0 stitches.

#### *Efficacy variables and outcomes*

Hernia recurrence was measured at 12 months post surgery, although no details were provided regarding the measurement of this outcome. Additionally, the evaluators considered 12 months to be an insufficient length of follow up for this outcome. Chronic pain (according to analog scale) and time taken to return to work were also reported; however, these outcomes were assessed in the overall patient rather than according to treatment group.

Due to the inability to separate this data based on treatment used, evaluators did not include and evaluate these data. Due to the lack of detailed reporting, the evaluators were unable to determine whether the methods used to measure efficacy outcomes affected the quality of the reported outcomes.

#### *Statistical considerations*

A total of 55 patients were included in this study, all of whom presented with bilateral hernia and received both treatments (fibrin glue on the right side and sutures on the left side). No power calculations were performed in order to determine the sample size required.

Patients were pseudo randomised to treatment group, undergoing mesh fixation using sutures for their right hernia and mesh fixation using Tissucol for their left hernia. It was unclear whether patients were aware which side received Tissucol. Further, the authors did not report whether the clinicians who undertook follow up analyses were blinded to the treatment used.

The statistical methods used in this study were not reported, and no statistical comparisons were made between treatment groups.

#### *Participant flow*

A total of 55 patients presenting with bilateral hernia were included in the study. The total number of patients screened for inclusion was not reported. Further, the study did not report whether any patients were lost to follow up or if there were any deviations from the protocol.

#### *Baseline data*

Due to the nature of the study (all patients receiving both treatments), patient demographics were identical for both groups. No mean age was provided but the age range was between 49–71 years. All patients were male and presented with bilateral inguinal hernias. Associated risk factors included obesity (56.3%), hypertension (32.7%) and obstructive pulmonary disease (20%). The data presented in this study may be used to inform on the effectiveness of Tissucol for mesh fixation in the treatment of inguinal

hernia in obese and non obese males aged 49–71 with bilateral inguinal hernia. These data cannot inform on the effectiveness of Tissucol in other patient populations.

#### *Results for the primary efficacy outcome*

There were no hernia recurrences in either group at 12 month follow up and no patients presented chronic pain.

#### *Results for other efficacy outcomes*

As secondary outcomes were not reported according to treatment group, the evaluators did not present these data.

#### **Study 3: Lau (2005)<sup>48</sup>**

This randomised controlled trial compared the clinical outcomes of simultaneous bilateral endoscopic totally extraperitoneal (TEP) inguinal hernia repair using either Tisseel or staples for mesh fixation. Patients presenting with inguinal hernias between July 2002 and February 2004 were included in the study. All surgeries were carried out in the Department of Surgery, University of Hong Kong Medical Centre. The trial was sponsored by a research fund from the Tung Wah group of Hospitals.

#### *Inclusion and exclusion criteria*

Detailed inclusion and exclusion criteria were described. The study was approved by the Ethics Committee of Tung Wah Hospital before commencement, and written informed consent was obtained from each patient prior to randomisation. The authors reported that all patients who presented with bilateral inguinal hernia were included in the study; however, the source of patient recruitment was not specified.

#### *Study treatments*

All patients underwent general anaesthesia and amoxicillin/clavulanate was administered intravenously on induction of anaesthesia. The number of surgeons performing the operations and their respective level of experience were not reported. The postoperative analgesic regime included oral analgesic (propoxyphene 50 mg) and paracetamol 325 mg, four times daily upon patient request.

Following randomisation, both treatment groups underwent the same surgical technique of endoscopic TEP inguinal hernioplasty, with mesh fixation method being the only difference. After reduction of the hernia sac and parietalisation of the spermatic cord to a length of approximately 4 cm, two 10 x 15 cm prolene meshes (Prolene Mesh, Ethicon Ltd, Somerville, NJ) were introduced, ensuring coverage of the posterior wall of the inguinal canal, deep inguinal ring and femoral ring on each side.

For the Tisseel group, the thrombin and sealer protein solution components of Tisseel were reconstituted at the commencement of surgery using a Fibrinotherm heating and stirring device (Baxter Healthcare Corporation). The two solutions were drawn into separate syringes, which were then fitted to the Duplocath 35 M.I.C. laparoscopic applicator (Baxter AG, Vienna, Austria). Of the 4 mL of Tisseel, 1 mL was applied over each Cooper's ligament, with the remaining 2 mL applied to the inferior edge and upper medial corner of the meshes.

An average of 2 mL of Tisseel was reported to have been applied per mesh. The mesh was held in position for a few minutes until the fibrin glue appeared opalescent on the television monitor.

For the Staple group, each mesh was anchored over the Coopers ligament along its medial edge and upper lateral corner using an endoscopic stapler (EMS Hernia Stapler, Ethicon

Ltd.). No staples were placed below the iliopubic tract lateral to the Cooper's ligament. The number of staples used per mesh was not reported.

#### *Efficacy variables and outcomes*

Efficacy outcomes were recurrence rate and chronic groin pain. A research assistant assessed chronic pain using a standardised questionnaire one year after the operation. Other efficacy outcomes included operative time (defined as the time from the skin incision to the placement of the last suture), length of hospital stay, and number of days required to resume normal outdoor activities and work. The authors did not provide any details of the assessors of these outcomes.

#### *Statistical considerations*

For sample size determination, the authors assumed an observed difference of 1.2 between the pain scores of the two treatment groups. This figure was based on a recent review by the authors, which presented a mean [SD] pain score on coughing after TEP surgery of  $3.4 \pm 1.86$ . It was calculated that a minimum sample size of 40 patients was required to identify a difference between treatment groups based on a significance level of 0.05 and an 80% power level. A total of 93 patients presenting with 186 inguinal hernias between July 2002 and February 2004 were included in the study and randomised to receive Tisseel (n=46) or staples (n=47) for mesh fixation. The majority of participants were inpatients (31/46 Tisseel patients and 37/47 Staple patients) and the remaining patients were outpatients (15/46 Tisseel patients and 10/47 Staple patients).

All patients were randomised on a 1:1 basis.

Data were analysed on an ITT basis. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared by the chi-square test or the Fisher exact test (when an expected value was less than 5). A p value < 0.05 indicated a statistically significant difference. Values were expressed as medians and interquartile range. Outcome measures were expressed with 95% confidence intervals (CI) when appropriate.

#### *Participant flow*

Of the 108 patients screened for inclusion in the study, fifteen patients were excluded prior to randomisation. Excluded patients were unsuitable for TEP (n=8), underwent concomitant procedures (n=5), refused to participate (n=1) or had dementia (n=1). The 93 remaining patients were randomly assigned to either the Tisseel (n=46) or staples (n=47) treatment groups. All patients received the allocated treatment, and no patients were lost to follow up. Both treatment groups comprised greater patient numbers than those required in the power calculation sample size (n=40). There were no reported deviations from the study protocol and all patients received the assigned treatment.

#### *Baseline data*

The authors stated that the two groups were comparable in sex, age, body weight and types of hernia; however, the statistical outcome of any between group differences was not provided. The mean ages of the Tisseel and Staple groups were 64 (range 55–71.3) 66 (range 55–76) years, respectively. All patients were male with the exception of a single female patient in the Staple group. Mean body weight was 60 (range 53.5–71.3) kg in the Tisseel group and 62 (range 58.0–69.7) kg in the Staple group (no statistical comparison provided). The authors did not present any data for smoking history, physical status or comorbidities. All patients presented with bilateral inguinal hernia, although the proportion of primary and recurrent hernias was not reported. Hernia type was classified

according to the Nyhus classification system (Table 5). Although the two groups appeared to be similar for hernia type, no statistical comparison was provided.

**Table 5: Distribution of hernia type based on the Nyhus classification system**

Hernia type	Tisseel	Staples
<b>II</b> Indirect hernia with dilated internal ring. Posterior wall intact	21 (22.8%)	16 (17%)
<b>IIIA</b> Direct inguinal hernia	52 (56.5%)	55 (58.5%)
<b>IIIB</b> Indirect inguinal hernia. Internal ring dilated. Posterior wall defective	14 (15.2%)	13 (13.8%)
<b>IIIC</b> Femoral hernia	0	1 (1.1%)
<b>IVA</b> Recurrent hernia (direct)	4 (4.3%)	8 (8.5%)
<b>IVB</b> Recurrent hernia (indirect)	1 (1.1%)	1 (1.1%)

Data from this study may inform on the effectiveness of Tisseel for mesh fixation in the treatment of bilateral inguinal hernia in males with a mean age of approximately 65 years. These data cannot inform on the effectiveness of Tisseel in other patient populations.

#### *Results for the primary efficacy outcome*

At a median follow up of 1.2 years there were no incidences of hernia recurrence in either treatment group. There was no significant between group difference in the incidence of chronic pain for the 78 patients assessed at median two year follow up (Tisseel 5/38, 13.2% (95% CI 2.5%–23.9%) and staple 8/40, 20% (95% CI 7.6%–32.3%)) (p=0.418).

#### *Results for other efficacy outcomes*

There was no significant between group difference for median operative time (Tisseel 76 [range 63.0–86.5] minutes and staple 75 [range 65.0–90.0] minutes) (p=0.348). All outpatients underwent day surgery and all were discharged on the same day for both treatment groups. For inpatients, there was no significant between group difference for the postoperative length of stay (Tisseel 1 [range 1–1] day and staple 1 [range 1–2] day) (p=0.428). There was no significant between group difference for the mean time to resume normal outdoor activities (3 days for both treatment groups, Tisseel range 2–5 days and staple range 2–4 days) (p=0.681).

A total of 35 patients were employed, although the number per group was not detailed. In these patients, there was no significant between group difference in the mean time taken to return to work (Tisseel patients 8 [range 4–10] days and Staple patients 6 [range 5–10] days) (p=0.915).

#### **Study 4: Lovisetto et al (2007)<sup>49</sup>**

This randomised controlled trial compared mesh fixation with Tissucol and staples in patients undergoing laparoscopic transabdominal preperitoneal hernioplasty for inguinal and femoral hernias. All procedures were performed on hospital inpatients by one of four surgeons at the General Surgery Unit at Sesto San Giovanni Hospital, Milano, Italy, between June 2003 and February 2005.

All patients provided written, informed consent prior to surgery. The study protocol was approved by the Ethical and Scientific Board of the Sesto San Giovanni Hospital. All deaths and life threatening complications were reviewed by an independent Endpoints Committee to determine whether the event was treatment related. The source from which patients were enrolled into the study was not reported.



### *Study treatments*

All procedures were standardised repairs performed by one of four surgeons with extensive experience in laparoscopic transabdominal preperitoneal (TAPP) hernia repair. Three of the surgeons were trained at the same surgery unit under the supervision of the leading skilled surgeon. The form of anaesthesia used was not reported. The authors did not report whether patients received antibiotic or antithrombogenic prophylaxis prior to surgery.

A 10 x 13 cm rectangular sheet of monofilament polypropylene mesh with large pores was used for all procedures in both treatment groups. For direct hernias, the sac was directly isolated and reduced. For indirect or femoral hernias, the sac was isolated and reduced.

In the Tissucol treatment group, the tails of the mesh were wrapped around the spermatic cord. Tissucol (1 mL) was applied to the mesh both posteriorly and anteriorly using a laparoscopic applicator (Duplotip, Baxter Healthcare, Milan, Italy). The Tissucol was applied to the entire perimeter of the mesh and in particular at the level of the superior margin, the 'triangle of disaster', and in proximity of the prevesical fat to ensure good adhesion. Slight pressure was applied using the Duplotip to ensure proper binding of the glue to the mesh, although the duration of this pressure was not reported.

An Endopath Multifeed Stapler 10 mm shaft with titanium staples was used in the Staple group. Three metal clips were positioned at the Cooper's ligament and pubic tubercle. Some fixations were carried out at the level of the deep inguinal ring, although the authors did not provide any reasons why these patients required a different approach. In these patients, the inferior branch of the mesh was passed beneath the spermatic cord to reconstruct the internal inguinal ring, and was then successively anchored to the superior branch with metal clips.

### *Efficacy variables and outcomes*

The primary efficacy outcome was hernia recurrence. Other reported outcomes included operative time, analgesic requirement, postoperative morbidity (based on a modified SF-36), post operative stay and time to return to normal activities.

The evaluators noted that following publication of this RCT in a peer reviewed journal, two surgical peers critiqued the authors' choice of outcome tools. Two correspondents considered that the modifications made to the SF-36 questionnaire included in this study were arbitrary and that no proof of the statistical validity and reliability of data were presented to support the modifications.<sup>64,65</sup> A further correspondent (also an author on this pivotal study), noted that the modified SF-36 questionnaire used in the study was a well defined and validated tool for assessing postoperative quality of life, based on a high correlation between the full SF-36 and the modified version as communicated at a previous conference.<sup>66</sup>

### *Statistical considerations*

The study was designed to detect a 20 mm difference in mean subjective pain scale scores between the two treatment groups with a sample of 200 patients, a power of 80% and an alpha error of 5%. As a total of 197 patients underwent surgery, the study had 79% power

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<sup>64</sup> Fortelny RH, Glaser KS, Petter-Puchner AH. Use of human fibrin glue (Tissucol) versus staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty. *Ann Surg* 2007; 246: 903.

<sup>65</sup> Novik B. Fibrin glue mesh fixation in hernia repair. *Ann Surg* 2007; 246: 906-8.

<sup>66</sup> Zonta S, Lovisetto F, Mauro L. Use of human fibrin glue (Tissucol) versus staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty. *Ann Surg* 2007; 246: 903-4.

to distinguish a difference of 13 mm in mean subjective pain scale scores, allowing a 2 sided Type 1 error rate of 5%.

The evaluators noted that this study appears to have been underpowered and may not have detected statistically significant between group differences for the outcome of pain.

All patients presenting at the institution who satisfied inclusion and exclusion criteria were eligible for random assignment. A total of 197 patients were allocated to treatment group using randomisation tables. Patients were unaware of treatment group prior to surgery and the surgeon performing follow up examinations was also unaware of the treatment received.

The modified SF-36 questionnaire was measured by multivariate analysis using the multivariate analysis of variance (MANOVA) test for repeated measures. Comparisons between the nominal variations were expressed as odds ratios. Continuous parametric variables were analysed by MANOVA and non continuous parametric variables were analysed using the Mann-Whitney U test.

#### *Participant flow*

All patients presenting at the institution who satisfied inclusion and exclusion criteria were eligible for random assignment. A total of 197 patients were enrolled in the study (Tissucol n=99, staple n=98). The number of patients screened against exclusion and inclusion criteria and then omitted from the study was not reported. In both groups, all patients received the treatment allocated to them. The authors did not report whether any patients were lost to follow up and all 197 patients formed the ITT cohort. Patients with bilateral hernias received treatment on both sides simultaneously, with one side chosen randomly to be the 'study hernia' to be included in the ITT analysis. The mean length of follow up was  $11.7 \pm 0.9$  months in the Tissucol group and  $11.6 \pm 1.2$  months in the Staple group.

#### *Baseline data*

Both groups of patients appeared to be demographically similar. However, the authors did not provide the outcome of any statistical analysis of between group differences. The mean age in the Tissucol patient and Staple patient groups were  $52.9 \pm 14.6$  years and  $53.2 \pm 12.6$  years, respectively. The male/female ratio was 87/12 for the Tissucol group and 89/9 for the Staple group. The American Society of Anaesthesiology (ASA) scores of patients were generally higher in the Staple group than the Tissucol group, although no statistical comparison was provided. Most patients presented with indirect inguinal hernias (76.7% Tissucol patients and 82.6% Staple patients, no statistical analysis provided). A high proportion of patients in both groups had comorbidities, most commonly hypertension, smoking and diabetes (no statistical analysis provided).

#### *Results for the primary efficacy outcome*

There was one recurrence in the Tissucol group. This was noted at one month follow up and was confirmed by echography. The recurrence was attributed to technical errors, as it was the only case where a mesh with large netting was not used. The authors suggested that this resulted in incomplete integration between the Tissucol and the mesh, leading to migration. Further, this patient was reported to have received a smaller mesh than other direct hernia patients, although the reasons for this were not noted. The patient underwent surgery to repair the recurrence and was recurrence free at 12 month follow up. There was no recurrence in the Staple group.

Incidence of pain, as reflected by mean VAS pain scores, was significantly lower in the Tissucol group than the Staple group at 3 ( $p < 0.001$ ) and 6 months ( $p < 0.001$ ). Three cases

of early nonspecific pain occurred in Tissucol patients and four cases occurred in Staple patients (no time period or statistical analysis provided). Additionally, one Tissucol patient reported late nonspecific pain as compared with five Staple patients (no statistical analysis provided).

The evaluators noted that this study appears to have been underpowered and may not have detected statistically significant between group differences for the outcome of pain.

#### *Results for other efficacy outcomes*

The mean operating time was significantly longer in the Tissucol group ( $53.8 \pm 7.6$  minutes) than the Staple group ( $39.6 \pm 7.6$  minutes) ( $p < 0.001$ ). The mean length of postoperative hospital stay was 1 day in both treatment groups. Tissucol patients returned to work significantly faster than Staple patients ( $7.9 \pm 1.3$  [range 5–11] days versus  $9.1 \pm 2.0$  [range 7–11] days) ( $p < 0.001$ ). Mean patient reported postoperative morbidity (measured using a modified SF-36 questionnaire) was significantly lower in Tissucol patients (23.2) than in Staple patients (22.6) at one month ( $p < 0.05$ ).

There were no significant between group differences for mean postoperative morbidity at three, six or 12 months. For the 'bodily pain' dimension, Tissucol patients reported significantly higher (better) mean scores than Staple patients at one, three and six months ( $p < 0.01$  at each). No other dimensions showed a significant between group difference at any time point.

Significantly more Tissucol patients than Staple patients reported the highest possible score for the 'bodily pain' ( $p < 0.001$ ) and 'pain interference with normal function' dimensions ( $p < 0.001$ ) at 1, 3 and 6 month follow up.

Five Staple patients required analgesics during physical activity at six month follow up ( $n=0$  for Tissucol;  $p > 0.05$ ). After six months, five Staple patients ( $n=0$  for Tissucol) required non steroidal anti-inflammatory drugs (NSAIDs); however, this difference was not statistically significant. Additionally, one Staple patient did not respond to NSAIDs one month post surgery.

#### ***Study 5: Olmi et al (2007a)<sup>51</sup>***

This was a randomised controlled study which compared pain outcomes in patients who received Tissucol or staples for mesh fixation during laparoscopic TAPP inguinal hernia repair. A total of 600 patients were included in the study (150 patients per treatment group). All operations were performed at the Surgical Department of San Gerardo Hospital, Monza, Italy between September 2001 and September 2004.

#### *Inclusion and exclusion criteria*

All patients under the age of 80 years were eligible for inclusion into the study, irrespective of hernia type. Excluded patients were those who were aged over 80 years, patients with contraindications to laparoscopic procedures (that is, severe cardiopulmonary disorders and portal hypertension) and patients electing not to undergo the TAPP procedure.

Informed consent forms were signed by each patient prior to the procedure. The study was conducted according to the ethical standards of the Committee on Human Experimentation and the ethical standards of the Helsinki Declaration of 1975.

#### *Study treatments*

All patients underwent laparoscopic TAPP inguinal hernia repair. A total of two expert surgeons performed the procedures, although the authors did not report details surrounding the type of anaesthesia used, or whether the hernia sac was reduced or

removed. The surgical technique used was identical in all treatment groups, with the exception of the method of mesh fixation.

Two 14 x 13cm L-shaped pieces of polypropylene mesh were used for each operation.

In the 150 Tisseel patients (222 hernias), either 1 mL (unilateral hernia) or 2 mL (bilateral hernia) of fibrin glue was applied using a 3 mm catheter (Duplotip; Baxter Healthcare). The mesh was fixed along its upper margin, from the Cooper's ligament to the 'triangle of disaster' and to the 'triangle of pain.'

In the Staple group, mesh was fixed using an EMS 10 mm shaft (n=150, 222 hernias), Protak (n=150, 189 hernias) or EndoANCHOR (n=150, 198 hernias). Two staples were placed medially and three laterally to epigastric vessels. A further two tacks were placed on the Cooper's ligament.

The peritoneum was closed over the mesh and the abdomen was not irrigated with any form of analgesic solution. All patients received one 100 mg dose of ketoprofen to manage postoperative pain.

#### *Efficacy variables and outcomes*

The primary efficacy outcome was hernia recurrence at one month post surgery.

The evaluators considered this to be too short to measure this outcome effectively.

The authors reported that objective data for this outcome were compiled for each patient; however, no further details surrounding these methods were provided. Further, it was unclear who the outcome assessors were and whether they had been provided with instructions for measuring outcomes.

Secondary outcomes assessed included length of hospital stay and time to return to work. No details were provided regarding measurement of length of postoperative stay or the time to return to work. Further, no details surrounding the outcome assessors were provided for these outcomes.

#### *Statistical considerations*

A total of 600 patients were enrolled into this study and randomised to one of four treatment groups (Tisseel fibrin glue or EMS, EndoANCHOR or Protak staples). No power calculations were reported to have been performed in order to determine the required sample size.

Patients were randomised to either EMS, EndoANCHOR or Protak Staple groups, or Tisseel fibrin glue groups on a 1:1:1:1 basis (n=150 per treatment group). The method of randomisation was not clearly stated, and the authors did not report whether there was any attempt to conceal treatment allocation from patients or outcome assessors. Both the patients and the surgeon conducting follow up visits were blinded to treatment group.

The authors did not state whether data were analysed according to ITT. Between group differences for postoperative pain, operating time and return to work were analysed using the Analysis of Variance (ANOVA) test and Tukey test for the *post hoc* analysis. Results were considered statistically relevant when  $p < 0.05$ , with a confidence interval of 95%.

#### *Participant flow*

The authors did not report the number of patients screened for enrolment. A total of 600 patients undergoing TAPP inguinal hernia repair were enrolled in the study, although the source of patient recruitment was not stated.

### *Baseline data*

A total of 803 hernias were treated in 600 patients (Tisseel 222, EndoANCHOR 198, EMS 194 and Protak 189). No significant between group differences were reported for age, gender or hernia type. The mean age per group ranged from 42 to 47 years and no patients aged below 18 or above 77 were enrolled. More than 96% of each group was male and more than 74% of patients in each group presented with a primary hernia. More Tisseel patients presented with bilateral hernias (37.5%) compared with the other treatment groups (EMS 29.3%, EndoANCHOR 32%, Protak 26%), although no statistical analysis was provided. No other patient data was reported in the study.

### *Results for the primary efficacy outcome*

A total of three recurrences occurred in the study, all of which occurred in the EMS group and were caused by the inferior lateral part of the mesh becoming unstuck. However, the use of EMS staples did not result in a significantly higher recurrence rate than Tisseel, or of EMS or EndoANCHOR staples ( $p > 0.05$  per group).

### *Results for other efficacy outcomes*

The mean operating time for unilateral hernias was significantly lower in the Tisseel group (30 [range 15–45] minutes) than the EMS (38 [range 20–50] minutes), EndoANCHOR (36 [range 15–50] minutes) and Protak (35 [range 18–50] minutes) groups ( $p < 0.05$ ).

Similarly, the mean operating time for bilateral hernias was significantly lower in the Tisseel group (50 [range 30–75] minutes) than the EMS (55 [range 37–80] minutes) and the EndoANCHOR (52 [range 35–80] minutes) groups ( $p < 0.05$ ).

The total length of hospital stay was significantly lower in the Tisseel group (1 [range 1–3] day) than in the EMS (1.2 [range 1–4] days), EndoANCHOR (1.1 [range 1–3] days) and Protak (1.1 [range 1–3] days) groups ( $p < 0.05$ ).

The mean time to resume work in the Tisseel group (5 [range 3–8] days) was significantly lower than in the EMS (9 [range 5–22] days), EndoANCHOR (7 [range 5–12] days) and Protak (9 [range 5–20] days) groups ( $p < 0.05$ ).

### **Other efficacy studies**

Eight 'other efficacy studies' were identified and evaluated. The evaluators have briefly presented these below, according to the surgical approach used (open or laparoscopic). None of the studies specified the formulation of Tisseel used.

Two studies used an open surgical approach, with either the Lichtenstein or the plug and patch technique. In the study that employed the Lichtenstein technique, a cohort of 56 patients was enrolled and randomised to receive either Tissucol ( $n=28$ ) or sutures ( $n=28$ ).<sup>42</sup> The authors failed to provide the outcome of any statistical analysis of demographic characteristics. The mean age of all patients included in the study was 67 years and no range was reported. All patients presented with a primary inguinal hernia which was neither recurrent nor considered an emergency case. No other study population or demographic data were presented and the mean volume of Tisseel used per hernia was not reported.

The primary effectiveness outcome was hernia recurrence, which was measured at mean 12 (range 1–18) months. No patients in either the fibrin glue or Suture groups experienced a hernia recurrence.

The evaluators considered the 12 month follow up to be insufficient for measuring this outcome.

In the study that employed the plug and patch technique, a cohort of 57 patients who underwent hernia repair using Tissucol for plug and mesh fixation were compared with a retrospective cohort of 57 demographically matched patients who underwent hernia repair using sutures for plug and mesh fixation.<sup>43</sup> The mean age of patients was  $60.8 \pm 12.6$  (range 35–80) years in the Tissucol group and  $59.2 \pm 13$  (range 33–79) years in the Suture group ( $p=0.5122$ ). Both treatment groups had identical numbers of male and female patients (53 male and three female). The mean BMI in the Tissucol group was  $24.7 \pm 3.2$  and for the Suture group was  $24.8 \pm 3.4$  ( $p=0.9781$ ). A similar number of patients per group were smokers (10/57 Tissucol patients and 11/57 suture patients). There was no significant difference in the activity levels of the two groups ( $p=0.8503$ ). All patients presented with primary inguinal hernia, with both groups consisting of 44 unilateral and 13 bilateral hernias. The hernia was located on the right side in 34/57 Tisseel patient and 30/57 suture patients, and on the left in 10/57 Tisseel patients and 10/57 suture patients ( $p=0.6323$ ).

A higher proportion of Tissucol patients had comorbidities (24/57 versus 20/57 suture patients), although this was not significant ( $p=0.5975$ ). Comorbidities included prostatism (Tisseel  $n=6$ , sutures  $n=5$ ), BPCO (Tisseel  $n=4$ , sutures  $n=6$ ) and constipation (Tisseel  $n=0$ , sutures  $n=2$ ). The mean volume of Tisseel used per hernia was not reported.

The primary efficacy outcomes were hernia recurrence and chronic pain, which were assessed at minimum 12 months in Tisseel patients and minimum 25 months in suture patients. No patients in either the fibrin glue or Suture groups experienced a hernia recurrence.

The evaluators considered the 12 month follow up in the Tisseel group to be insufficient for measuring this outcome.

During follow up, reports of chronic inguinal pain were significantly lower in the Tisseel group ( $n=2$ ; 1 mild, 1 moderate) (3.5%) than the Suture group ( $n=13$ ; 8 mild, 3 moderate, 2 severe) (22.8%) ( $p=0.042$ ). It should be noted, however, that the mean follow up was longer in the Suture group as this group was a historical series ( $40 \pm 9.2$  versus  $25.2 \pm 8.8$  months;  $p<0.0001$ ).

Secondary outcomes included the time required to return to normal daily activities, length of hospital stay and operative time. The authors reported that the mean operative time was significantly lower in the Tisseel group than the Suture group for both unilateral hernia ( $44 \pm 9$  mins, range 28–70 versus  $54 \pm 11$  mins, range 30–75) ( $p=0.0017$ ) and bilateral hernia ( $82 \pm 10$ , range 65–95 versus  $98 \pm 10$  mins, range 70–110) ( $p=0.0008$ ). The length of hospital stay was significantly shorter in the Tisseel group ( $1.8 \pm 0.9$  versus  $2.4 \pm 0.7$  days) ( $p<0.0001$ ).

The remaining six studies used a laparoscopic surgical approach. Two of these studies used the TAPP technique.<sup>36, 46</sup> Both studies failed to report the outcome of any statistical analysis of baseline demographic characteristics and the evaluators could not be sure that the treatment groups were comparable at baseline. One study used staples as a comparator to Tisseel and enrolled 68 patients per treatment group. Mostly males were enrolled, and 6/68 Tisseel patients and 4/68 Staple patients were female. The mean age of patients was 45–48 years, and they presented most commonly with indirect inguinal hernias (a small number of patients presented with direct inguinal hernias, or femoral hernias).<sup>46</sup> The treatment groups were described as similar for age, gender, hernia type and length of follow up. No details were provided regarding BMI, smoking history or physical status.

The second study used autologous fibrin sealant as a comparator to Tisseel and enrolled 20 Tisseel patients and 10 autologous fibrin sealant patients.<sup>36</sup> Mostly males were

enrolled, and 1/20 Tisseel patients and 1/10 autologous fibrin sealant patients were female. The mean age of patients was 47–50 years and autologous fibrin sealant patients presented with inguinal hernias. Tisseel patients presented with undefined, although most likely inguinal, hernias. The mean BMI was 27 in Tissucol patients and 25 in autologous fibrin sealant patients, and the mean ASA score was 1.7 for each treatment group. One study used a 2 mL kit of Tisseel<sup>46</sup>, and the other study used 1 mL of Tissucol for hernias <3.5 cm in size and 2 mL for hernias >3.5 cm.<sup>36</sup>

The first primary efficacy outcome was the incidence of hernia recurrence, which was assessed over a mean of 19 months in one study<sup>46</sup>, and at mean nine months in Tisseel patients and mean seven months in autologous fibrin sealant patients in the other study.<sup>36</sup> In both studies, no hernia recurrence occurred in either treatment group.

The evaluators considered the 12 month follow up to be insufficient for measuring this outcome.

The second primary efficacy outcome was the incidence of chronic pain, which was assessed over a mean of 19 months one study<sup>46</sup>, and at three months in the other study.<sup>36</sup> In both studies, there was no chronic pain in either group.

Secondary outcomes included length of postoperative stay and operative time. One study reported that the mean operative time was significantly higher in the Tisseel group (35 minutes, range 22–65) than in the Staple group (25 minutes, range 14–50) ( $p < 0.05$ ). The other study found that operative time was lower in Tisseel patients (no statistical analysis provided). In one study all patients were discharged within 24 hours of the operation, and in the second the mean postoperative hospital stay was three days in Tissucol patients and 2.9 days in autologous fibrin sealant patients (no statistical analysis provided).

One study used the miniTAPP technique.<sup>52</sup> No inclusion or exclusion details were reported, and the source from which patients were enrolled into the study was not revealed. A total of 250 patients with 426 inguinal hernias received Tissucol for mesh fixation, and were compared with a historical series of 245 patients with groin hernias received tacks for mesh fixation.

*Although the proposed indication is for mesh fixation in hernia repair, as an alternative or adjunct to sutures or staples, the evaluators noted that expert clinical opinion advises that tacks are currently used in Australian practice. Additionally, the sponsor did not provide PICO criteria to inform on the appropriate comparators to Tisseel. Hence, the evaluators included and evaluated this study.*

No baseline demographic data were provided for the Tack group. However, the authors stated that there were no statistical differences between the groups at baseline for demographic characteristics, and the type and side of the hernia. The mean age of Tissucol patients was 52.6 (range 31–83) years. The Tissucol group included 15 females and 235 males who presented with 176 bilateral and 74 unilateral hernias. Of these, 45 hernias were recurrent and 205 were primary. Six patients in the Tissucol group had comorbidities (umbilical hernia  $n=1$ , spermatic vein bindings for varicoceles  $n=3$ , section of adhesion  $n=1$  and renal cyst  $n=1$ ) and underwent procedures performed in the same setting as the hernia repair. The authors did not report on any comorbidities in the Tack group. The mean volume of Tissucol used per hernia was not reported.

A primary outcome was hernia recurrence, which was measured over an undefined period. The rate of recurrence was significantly lower in the Tissucol group (0/426) than the Tack group (4/245, 1.6%) ( $p=0.035$ ). The second primary outcome was chronic pain. At three months, there were no significant between group differences in mild pain (two Tissucol patients and one Tack patient) ( $p > 0.05$ ).

Secondary outcomes included operative time, time to return to normal activities and patient satisfaction. Generally, the outcomes reported by Tisseel patients were not significantly different to those reported by Tack patients. Approximately 90% of patients were reported to have returned to normal activity within seven days and all patients had returned to normal activity within 14 days. All patients were reported to have been satisfied with the surgery at the three month follow up. Additionally, no difficulty was encountered during the preparation or application of the fibrin glue.

The remaining three studies used the TEP technique.<sup>50, 53, 54</sup>

One study used tacks as a comparator to Tisseel and enrolled six male patients (with nine hernias) in the Tisseel group and 96 male patients in the Tack group.<sup>22</sup>

*Although the proposed indication is for mesh fixation in hernia repair as an alternative or adjunct to sutures or staples, the evaluators noted that expert clinical opinion advises that tacks are currently used in Australian practice. Additionally, the sponsor did not provide PICO (Population, Indication, Comparator and Outcome) criteria to inform on the appropriate comparators to Tisseel. Hence, the evaluators included this study.*

This study failed to report the outcomes of any statistical analysis of baseline demographic characteristics. The mean age was 61 (range 40–76) years in Tisseel patients and 58 (range 26–87) years in Tack patients. The mean ASA score was 1.4 in the Tack group while five Tisseel patients were ASA II and one patient was ASA I. More patients in the Tack group (n=56, 58.3%) than in the Tisseel group (n=3, 50%) presented with bilateral hernia (no statistical analysis provided). One Tisseel patient (16.7%) and nine Tack patients (9.6%) presented with recurrent hernia (no statistical analysis provided).

The second study used staples as a comparator to Tisseel and enrolled a total of 133 patients with 186 hernias. The number of patients enrolled per treatment group was not defined; however, 173 hernias were followed up, 86 of which had been repaired using Tisseel and 87 repaired using staples.<sup>53</sup> This study did not provide the outcome of any statistical analysis of baseline demographic characteristics. The mean age was 54.7 (range 27–80) years in Tisseel patients and 57 (range 20–79) years in Staple patients. All patients were male and all hernias were primary. There were a total of 48 bilateral and 77 unilateral hernias; however, these were not separated by treatment group. No other patient data were reported (such as body mass index (BMI), smoking history and physical status).

The third study used staples as a comparator to Tisseel and enrolled 66 Tisseel patients and 102 staple patients.<sup>54</sup> There were no significant differences between the treatment groups regarding age, hernia type (inguinal or femoral) or side of the hernia at baseline. The mean age was  $55.6 \pm 17$  years in the Tisseel group and  $55.8 \pm 15.7$  years in the Staple group (p value not provided). Significantly more females were reported to have been enrolled in the Staple group (16/102) than in the Tisseel group (2/66) (p value not provided). Seven of the 66 Tisseel patients (10.6%) and 15 out of the 102 Staple patients (14.7%) presented with a recurrent hernia, although this was not significant (p value not provided). Three Staple patients had comorbidities (incisional hernia repair n=1, haemorrhoidectomy n=1 and drainage of ascites n=1). Comorbidity data were not reported for Tisseel patients. All studies reported the mean volume of Tisseel applied per patient, which ranged from 2 mL for unilateral hernias up to 10 mL for bilateral hernias.

The primary outcome was hernia recurrence, which was reported for up to 40 months<sup>50</sup> (mean of 15.3 months<sup>53</sup>); mean  $23.9 \pm 11.3$  months in Tisseel patients and  $28.3 \pm 10.9$  months in Staple patients.<sup>54</sup> One study reported that there were no recurrences in either group<sup>50</sup>, and the other studies reported that recurrence occurred more commonly in



Staple patients than in Tisseel patients but no statistical analysis was performed for this outcome.<sup>54</sup>

Chronic pain was reported for up to 40 months<sup>50</sup> (mean 15.3 months<sup>53</sup>), or more than three months post surgery.<sup>54</sup> In one study, two patients in the Tisseel group reported pain (one mild (and not related to hernia surgery), one insignificant), and 30 patients in the Staple group reported pain (three moderate, 11 mild, 16 insignificant).<sup>50</sup> In the second study, chronic inguinal pain was defined as any postoperative pain persisting for longer than three months after surgery. It was significantly lower in the Tisseel group ( $p=0.002$ ).<sup>53</sup> Chronic pain was present in 4/86 Tisseel hernias (4.7%) and 18/87 Staple hernias (20.7%). Ten of the 18 Staple group cases required local infiltrations of anaesthetics. None of the Tissucol group cases required local infiltrations of anaesthetics. In the third study, fewer patients in the Tisseel group ( $n=3$ ) than the Staple group ( $n=15$ ) reported pain in the groin area more than three months post surgery ( $p=0.037$ ).<sup>54</sup>

Secondary outcomes included operative time, length of postoperative hospital stay and foreign body sensation. Generally, statistical analyses for these outcomes were not provided. The mean length of postoperative hospital stay ranged from 0 days to  $1.5 \pm 1.7$  days in Tisseel patients and from 1.4 days to 2.3 days in Staple patients.

#### **Evaluator's conclusions on clinical efficacy of Tisseel for mesh fixation in hernia repair, as an alternative or adjunct to sutures or staples**

The proposed indication for Tisseel is for mesh fixation in hernia repair as an alternative or adjunct to sutures or staples. Evidence of the efficacy of Tisseel for this indication was obtained from a total of five pivotal efficacy studies (including one unpublished pivotal study provided by the sponsor). These studies were classified as Level II or III-1 according to the NHMRC hierarchy of evidence<sup>67</sup>.

Patients were reported to have been randomised in four studies and appeared to have been pseudorandomised in the remaining study.<sup>47</sup> Allocation concealment was reported to have been achieved in three studies<sup>44, 44, 49</sup> but was not reported upon for the two remaining studies. All five studies employed an active comparator; sutures<sup>44, 47</sup> or staples.<sup>48, 49, 51</sup> In three studies, both the patient and outcome assessor were blinded to treatment allocation. The remaining two studies failed to report whether blinding was attempted.<sup>44, 49, 51</sup> Power calculations for sample size determination were reported to have been conducted in three of the five studies, two of which were derived from peer reviewed clinical data. However, one study enrolled fewer than the indicated number of patients and therefore appears to have been underpowered. The majority of the studies reported some detail on the statistical methods used; however, none provided an *a priori* non inferiority margin. Where reported, between group differences were considered statistically significant when  $p < 0.05$ . Additionally, three studies provided 95% confidence intervals (CIs). All five studies provided raw efficacy data to allow readers to interpret clinical significance independently of statistical significance. Three studies stated that between group analyses were performed on the ITT population. One of these studies also provided PP analyses for selected efficacy outcomes. The evaluators noted that outcome assessments were generally conducted by patients, with or without additional assessments conducted by surgeons or research assistants. All five studies reported the measurements for outcomes identified in the protocol and in no study report was it stated that there were any post hoc amendments to the methods of outcome measurement.

No similar biological medicinal products were studied in the five studies. One 'other' efficacy study compared Tisseel with another type of fibrin sealant (autologous). No

<sup>67</sup> [http://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/evidence\\_statement\\_form.pdf](http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf)

studies reported on the efficacy of Tisseel compared with any other known fibrin sealants, such as Evicel.

The evaluators noted that expert clinical opinion indicates that hernia recurrence and the incidence of chronic pain are the most clinically appropriate outcome measures for the indication of mesh fixation in hernia repair. All five studies measured at least one of these outcomes. Expert clinical opinion further advises that chronic pain may be defined as pain persisting for more than three months post surgery. Three studies reported outcomes for chronic pain and these were reported between six and 12 months post surgery.<sup>44, 48, 49</sup> The evaluators considered this to be sufficient long term data for measuring chronic pain. All five studies reported outcomes for hernia recurrence. Expert clinical opinion advises that although early recurrence usually occurs within three to four months, longer term recurrence may occur many years later. Generally, the studies reported on this outcome at up to 12 months post surgery, which the evaluators consider to be insufficient for long term data. Where reported, surgeons appear to have found Tisseel to be easy to use.

#### ***Efficacy of Tisseel for mesh fixation during hernia repair - Open surgical approach***

Two pivotal studies reported on the efficacy of Tisseel in patients undergoing inguinal hernia repair using the open surgical approach and the Lichtenstein technique.<sup>44, 47</sup> Both studies used sutures as an active comparator to Tisseel, which is consistent with current Australian practice. In one study, recurrence had occurred in 0.63% of Tisseel patients and 1.25% of suture patients at 12 month follow up (no statistical analysis provided). In the other study no recurrences occurred in either group after the (mean) 12 month follow up. The recurrence rate in both pivotal studies was lower than those reported in a 2008 Cochrane review of patients undergoing open repair of inguinal hernia (2.76%–3.34%).<sup>63</sup> Only one study reported on chronic pain; at 12 month follow up there were no significant between group differences for mean pain score or the number of patients reporting pain.<sup>44</sup> Regarding secondary outcomes, the effect of Tisseel was generally favourable compared with sutures for numbness, groin discomfort, patient satisfaction, length of hospital stay and time to return to normal activities.

Overall, the evaluators considered that the primary efficacy outcomes reported in these studies were not supportive of Tisseel's superiority over sutures for mesh fixation in open, Lichtenstein inguinal hernia repair. However, these data did not indicate that Tisseel was significantly worse than sutures for this indication. The evaluators considered that the statistically significant improvements in numbness and groin discomfort outcomes reported in one study were supportive of Tisseel's superiority over sutures for mesh fixation in open Lichtenstein inguinal hernia repair.<sup>44</sup>

#### ***Efficacy of Tisseel for mesh fixation during hernia repair - laparoscopic surgical approach***

Two pivotal studies reported on the efficacy of Tisseel in patients undergoing inguinal or femoral hernia repair using the laparoscopic surgical approach and the TAPP technique.<sup>49, 51</sup> Both studies used staples as the active comparator to Tisseel which is inconsistent with current Australian practice where tacks are predominantly used. One recurrence was reported to have occurred in a Tisseel patient and neither study reported that recurrence was significantly lower in Tisseel patients than in suture patients. Chronic pain was reported by one study and was significantly lower in Tisseel patients than suture patients at three and six months. Regarding secondary outcomes, when compared with Staple patients, Tisseel patients had a significantly longer mean operating time in one study and a significantly shorter mean operating time in the other study. Generally, the effect of Tisseel was favourable compared with staples for length of hospital stay and was equivalent or favourable compared with staples for the time taken to return to work.

Overall, the evaluators considered that the recurrence outcomes reported in the pivotal studies were not supportive of Tisseel's superiority over staples for mesh fixation in laparoscopic TAPP inguinal hernia repair. However, the data did not indicate that recurrence outcomes were significantly worse in Tisseel patients than Staple patients for this indication. The significant improvement in chronic pain outcomes, and in length of hospital stay and time taken to return to work, were supportive of Tisseel's superiority over staples.

The remaining pivotal study reported on the efficacy of Tisseel in patients undergoing inguinal or femoral hernia repair using the laparoscopic surgical approach and the TEP technique.<sup>48</sup> This study used staples as the active comparator to Tisseel which is inconsistent with current Australian practice where tacks are predominantly used. At the median 1.2 year follow up there were no incidences of hernia recurrence in either treatment group and there was no significant between group difference in the incidence of chronic pain. Regarding secondary outcomes, generally, the effect of Tisseel was equivalent compared with staples for operative time, length of postoperative hospital stay and the time taken to return to normal activities.

Overall, the evaluators considered that the recurrence and chronic pain outcomes and the secondary efficacy outcomes reported in this study were not supportive of Tisseel's superiority over staples for mesh fixation in laparoscopic TEP inguinal hernia repair.

When considering the proposed indication (mesh fixation during hernia repair, as an alternative or adjunct to sutures or staples), the evaluators considered that the external validity of the provided pivotal efficacy studies was poor. Subpopulation analyses were not provided and the vast majority of studied patients were middle aged males with bilateral or unilateral primary inguinal hernias. Although one pivotal study reported that patients with recurrent hernias were enrolled, no subgroup analysis was conducted for these patients. Very few patients underwent femoral hernia repair and no other hernia types were studied. Expert clinical advice indicates that the evidence of Tisseel's efficacy in inguinal hernias may broadly be generalised to other spontaneous abdominal wall hernias (that is, femoral and umbilical hernias) but not to incisional hernias due to the higher rate of recurrence. Hence, the efficacy of Tisseel for mesh fixation in incisional hernias remains uninformed by current evidence.

Additionally, the pivotal efficacy studies generally excluded patients who were deemed unsuitable to receive the surgical technique of interest or those with contraindications to surgery or general anaesthesia (for example, severe cardiopulmonary disorders, ASA class IV-V, portal hypertension, bowel obstruction/strangulation/perforation, peritonitis, local/systemic infection). No studied patients were aged less than 18 years and very few were aged over 80 years and no other special risk patients were studied. Patients who required concomitant abdominal surgery, or who were enrolled in another trial, were generally excluded. The efficacy of Tisseel for mesh fixation in hernia repair in these patients is unclear.

The evaluators noted that a variety of additional factors may contribute to the success of mesh fixation for hernia repair procedure and subsequent incidence of chronic pain and recurrence and other efficacy outcomes. These may include the type and nature of mesh used (for example, polypropylene (PPE), polytetrafluoroethylene (pTFE), lightweight, biological, pore size, bioabsorbability, barrier protection), the size of mesh overlap of the hernia edge and specific patient demographics (for example, age, BMI, smoking status, comorbidities, unique physiologies). Generally, these factors were not reported upon in sufficient detail in the pivotal efficacy studies.

The sponsor noted that there were no paediatric data/formulations for this product but did not provide a paediatric development program. The pivotal studies did not inform on optimal dose regimens for Tisseel when used for mesh fixation during hernia repair, although the volume of Tisseel used per patient ranged from 1 mL up to 4 mL (for bilateral hernias). The formulation of Tisseel used was not specified. As no special risk patients were included, no dose adjustment recommendations for these groups may be made. Tisseel appears to have been applied in a once off manner, rather than repeatedly.

Regarding the *Clinical Overview* document provided by the sponsor, the evaluators noted several areas of disagreement, which are detailed below.

The sponsor nominated the following outcomes measures for the effectiveness of Tisseel for mesh fixation in hernia repair:

- technical outcomes, including operating time, days of hospitalisation, days to resume normal activity, and cost
- intra and postoperative complications, including pain and the incidence of haematomas or seromas
- chronic complications, including pain and hernia recurrence rate.

The evaluators disagreed with the sponsor's selection of effectiveness outcome measures for the proposed indication. The evaluators considered that hernia recurrence and the incidence of chronic pain are the most clinically appropriate outcome measures for this indication. The evaluators have more appropriately assessed intra- and postoperative complications as safety outcomes rather than efficacy outcomes and considered the technical outcomes to be secondary effectiveness measures.

The evaluators considered that the sponsor has erroneously linked the technical outcomes (secondary efficacy outcomes) with the acceptance of Tisseel by surgeons. The evaluators suggested that the sponsor amends this paragraph in order to remove the link between technical outcomes and surgeons' acceptance of Tisseel. The evaluators agreed that, where reported, surgeons found Tisseel to be easy to use and suggested that the sponsor reports this independently of the technical outcomes.

The sponsor reported that chronic pain was lower in Tisseel patients in six studies. However, the sponsor did not delineate between the lower and higher quality studies. The evaluators considered that the sponsor has drawn an efficacy conclusion based on low level evidence, despite the availability of high level evidence. When considering the best available evidence (pivotal efficacy studies), Tisseel only appeared to confer a significant benefit for chronic pain in TAPP hernia repair. No other significant benefits were demonstrated for this outcome in the remaining four pivotal efficacy studies.

The evaluators considered that the sponsor's conclusion on efficacy extrapolates the available evidence (efficacy of Tisseel in middle aged male patients with inguinal hernias) to all patient populations and hernia types. The sponsor did not present any evidence for the efficacy of Tisseel in obese, female, paediatric or elderly inguinal hernia patients, or for non inguinal hernias in any patient population. Although the majority of hernias separated in Australian public and private hospitals between July 1998 and July 2008 were inguinal (439,238 of 793,239 hernias), the remaining non inguinal hernia patients represent a large proportion of the Australian hernia population, in which there is no evidence of the effectiveness of Tisseel.<sup>68</sup> Expert clinical advice indicates that the evidence of Tisseel's

<sup>68</sup> Australian Institute of Health and Welfare, *Separation statistics by principal diagnosis in ICD-10-AM, Australia, 1998-99 to 2006-07*, Australian Institute of Health and Welfare, Canberra, 2011; available from <http://www.aihw.gov.au/data-cube/?id=10737418525&libID=10737418524>.

efficacy in inguinal hernias may broadly be generalised to other spontaneous abdominal wall hernias (that is, femoral and umbilical hernias) but not to incisional hernias due to the higher rate of recurrence. The sponsor reported effectiveness outcomes for patients with abdominal incisional hernias; however, the evaluators considered the studies which informed on this population to be ineligible for inclusion in this evaluation as the fibrin sealant was used for wound closure rather than mesh fixation and did not meet the sponsor's own inclusion criteria. Hence, the efficacy of Tisseel for mesh fixation in incisional hernias remains uninformed by current evidence. Importantly, expert clinical opinion indicates that the rate of recurrence is higher in incisional hernias than in non iatrogenic abdominal wall hernias.

Regarding the comparison of results in sub populations, the sponsor noted that the percentage of males was very high in the inguinal hernia studies. The evaluators do not consider this to be an appropriate sub population, as inguinal hernias generally occur in males.

## **Safety**

### **Studies providing evaluable safety data**

The studies providing evaluable safety data are summarised in Table 6.

**Table 6: Included safety studies**

<b>Study details</b>	<b>Study type</b>
Campanelli (2009) <sup>44</sup>	Pivotal efficacy study
Hidalgo et al (2005) <sup>47</sup>	Pivotal efficacy study
Lau (2005) <sup>48</sup>	Pivotal efficacy study
Lovisetto et al (2007) <sup>49</sup>	Pivotal efficacy study
Olmi et al (2007a) <sup>51</sup>	Pivotal efficacy study
Benfatto et al (2006) <sup>42</sup>	Non-pivotal efficacy study
Benizri et al (2006) <sup>43</sup>	Non-pivotal efficacy study
Ceccarelli et al (2008) <sup>46</sup>	Non-pivotal efficacy study
Novik et al (2006) <sup>50</sup>	Non-pivotal efficacy study
Santoro et al (2007) <sup>52</sup>	Non-pivotal efficacy study
Schmidt and Langrehr (2006) <sup>36</sup>	Non-pivotal efficacy study
Schwab et al (2006) <sup>53</sup>	Non-pivotal efficacy study
Topart et al (2005) <sup>54</sup>	Non-pivotal efficacy study
Agresta and Bedin (2008) <sup>55</sup>	Case series (safety only)
Canonico et al (2007) <sup>45</sup>	Case series (safety only)
Canonico et al (2005) <sup>32</sup>	Case series (safety only)
Canziani et al (2009) <sup>56</sup>	Case series (safety only)
Descottes and Bagot d'Arc (2009) <sup>57</sup>	Case series (safety only)
Fine (2006) <sup>58</sup>	Case series (safety only)
Fortelny et al (2008) <sup>33</sup>	Case series (safety only)
Olmi et al (2007b) <sup>34</sup>	Case series (safety only)
Olmi et al (2007c) <sup>35</sup>	Case series (safety only)

### **Other studies evaluable for safety only**

The following nine studies were included for safety only. They were not included in the efficacy evaluation as they are all case series and cannot provide comparative efficacy data. Of the nine studies, six evaluated inguinal hernia repair (using either the open or laparoscopic approach), two evaluated incisional hernia repair (using either the open or laparoscopic approach), and one evaluated groin hernias using an open, modified Lichtenstein technique.

#### ***Agresta and Bedin (2008)<sup>55</sup>***

This was a retrospective case series in which adults undergoing laparoscopic inguinal hernia repair received Tisseel for mesh fixation. Study participants were patients at the Civil Hospital in Vittorio Veneto, Italy, although it was unclear whether they were consecutively or selectively enrolled. A total of 11 patients were enrolled and all completed the study. Adverse events (AEs) were recorded immediately after the surgical procedure and at 10 day, two month and 12 month follow up. This study was not included

in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Canonico et al (2007)***<sup>45</sup>

This was a prospective case series in which patients undergoing open (Lichtenstein) primary groin hernia repair received Tisseel for mesh fixation. Study participants were professional soccer players affected by chronic groin pain and referred for inguinal open surgical exploration. Patients were consecutively enrolled. A total of 16 patients were enrolled and all completed the study. AEs were recorded at seven days post surgery, monthly for three months post surgery, and then at one year post surgery. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Canonico et al (2005)***<sup>32</sup>

This was a prospective case series in which adults undergoing open (suture free Lichtenstein) inguinal hernia repair received Tisseel for mesh fixation. The authors did not report the source from which patients were recruited into the study, although patient enrolment was consecutive. A total of 80 patients were enrolled but the authors did not report whether any patients were lost to follow up. AEs were recorded at seven days, six months and 12 months post surgery. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Canziani et al (2009)***<sup>56</sup>

This was a case series in which adults undergoing recurrent incisional hernia repair (via the Rives technique) received Tisseel for mesh fixation. It was unclear whether this was a prospective or retrospective case series, and the source from which patients were recruited into the study was not reported. Additionally, it was unclear whether patients were consecutively or selectively enrolled. A total of 40 patients were enrolled and all appeared to complete the study. AEs were recorded at one week, one, three and six months, and one and five years post surgery. The median length of follow up was one year. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Descottes and Bagot d'Arc (2009)***<sup>57</sup>

This was a prospective, multicentre case series in which adults undergoing laparoscopic or open tension free inguinal hernia repair received Tisseel for mesh fixation. Study participants were sourced via contacting fifty public or private French general surgeons who performed at least 100 hernioplasties annually and were already using Tisseel for mesh fixation. It was unclear whether each surgeon consecutively or selectively enrolled patients. A total of 1201 patients were enrolled (526 received the open approach and 675 received the laparoscopic approach), and all completed the study. AEs were recorded at median 34 days post surgery. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Fine 2006***<sup>58</sup>

This was a case series in which adults undergoing laparoscopic inguinal hernia repair received Tisseel for mesh fixation. It was unclear whether this was a prospective or retrospective case series, and the source from which patients were recruited into the study was not reported. Additionally, it was not explicitly stated that patients were consecutively enrolled. A total of 38 patients with 45 primary and six recurrent inguinal hernias were enrolled but the authors did not report whether any patients were lost to follow up. AEs were recorded at two weeks and six weeks post surgery. This study was not

included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Fortelny et al (2008)***<sup>33</sup>

This was a case series in which adults undergoing laparoscopic TAPP primary inguinal or femoral hernia repair received Tisseel for mesh fixation. It was unclear whether this was a prospective or retrospective case series. Study participants were patients at the Department of Surgery, Wilhelminenspital der Stadt Wien, Austria, and were consecutively enrolled. A total of 11 patients were enrolled but the authors did not report whether any patients were lost to follow up. AEs were recorded daily during the patient's hospital stay and then at 10 days, three months and one year post surgery. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Olmi et al (2007b)***<sup>34</sup>

This was a case series in which adults undergoing laparoscopic incisional, umbilical, spigelian or epigastric hernia repair received Tisseel for mesh fixation. It was unclear whether this was a prospective or retrospective case series and the source from which patients were recruited into the study was not reported. Additionally, it was not explicitly stated that patients were consecutively enrolled. A total of 40 patients were enrolled but the authors did not report whether any patients were lost to follow up. AEs were recorded at day seven, week six, and six and 12 months post surgery. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

***Olmi et al (2007c)***<sup>35</sup>

This was a case series in which adults undergoing laparoscopic inguinal hernia repair received Tisseel for mesh fixation. It was unclear whether this was a prospective or retrospective case series and the source from which patients were recruited into the study was not reported. The authors stated that patients were selectively enrolled. A total of 60 patients with 61 hernias were enrolled but it was not reported whether any patients were lost to follow up. AEs were recorded at seven days, one, three and six months, and one and two years post surgery. This study was not included in the efficacy evaluation due to the substantial amount of comparative efficacy evidence that was available.

**Patient exposure**

A total of 22 studies were available to inform on the safety of Tisseel when used for mesh fixation in hernia repair (Table 7).



**Table 7: Exposure to Tisseel and comparators in clinical studies**

Study type	Controlled studies			Uncontrolled studies	Total fibrin sealant
	Fibrin sealant	Sutures	Staples	Fibrin sealant	
<b>Pivotal</b>					
Campanelli (2009) <sup>44</sup>	158	158			
Hidalgo et al (2005) <sup>47, a</sup>	55	55			
Lau (2005) <sup>48</sup>	46		47		
Lovisetto et al (2007) <sup>49</sup>	99		98		
Olmi et al (2007a) <sup>51, b</sup>	150		450		
<b>Other</b>					
Comparative:					
Benfatto et al (2006) <sup>42</sup>	28	28			
Benizri et al (2006) <sup>43</sup>	57	57			
Ceccarelli et al (2008) <sup>46</sup>	68		68		
Novik et al (2006) <sup>50</sup>	6		96		
Santoro et al (2007) <sup>52</sup>	250		245		
Schmidt and Langrehr (2006) <sup>36, c</sup>	20				
Schwab et al (2006) <sup>53, d</sup>	86		87		
Topart et al (2005) <sup>54</sup>	66		106		
Case series:					
Agresta and Bedin (2008) <sup>55</sup>				11	
Canonico et al (2007) <sup>45</sup>				16	
Canonico et al (2005) <sup>32</sup>				80	
Canziani et al (2009) <sup>56</sup>				40	
Descottes and Bagot d'Arc (2009) <sup>57</sup>				1201	
Fine (2006) <sup>58</sup>				38	
Fortelny et al (2008) <sup>33</sup>				11	
Olmi et al (2007b) <sup>34</sup>				40	
Olmi et al (2007c) <sup>35</sup>				60	
<b>Total</b>	<b>1089</b>	<b>298</b>	<b>1197</b>	<b>1497</b>	<b>2586</b>

a Same patients in both groups (all had bilateral hernias with sutures used on the right side and Tisseel on the left side).

b Three staple types used (Protak, EMS or EndoANCHOR) with 150 in each group.

c The 20 Tissucol patients were compared to 10 patients who had an alternative, autologous fibrin sealant (Vivostat).

d One study<sup>25</sup> only reported group sizes by number of hernias, rather than number of patients.

A total of 2586 patients received Tisseel for mesh fixation during hernia repair. Where reported, the dosage ranged from 1 mL to 10 mL per patient. Tisseel appeared to have been used in a one off manner and not used repeatedly.

## Adverse events

### *All adverse events (irrespective of relationship to study treatment)*

For the following studies that reported adverse events (AEs), pain occurring less than three months after surgery was considered postoperative pain and was included as a safety outcome, while pain occurring more than three months after surgery was considered chronic pain and was included as an efficacy outcome. Case series were an exception; for these studies chronic pain was included in the safety section as it was not reported elsewhere.

#### *Pivotal efficacy studies*

One unpublished pivotal efficacy study was presented by the sponsor.<sup>44</sup> This study contained the most detailed reporting of safety outcomes. An additional four pivotal efficacy studies reported safety outcomes.<sup>47, 48, 49, 51</sup>

In the unpublished study a total of 108 AEs were experienced by 56 Tisseel patients and a total of 83 AEs were experienced by 56 suture patients.<sup>44</sup>

The authors stated that there was no significant between group difference for the number of patients with at least one AE; however, the evaluators considered that the authors failed to present all complications as AEs; seromas, haematomas and bruising/ecchymosis were classified as 'wound healing complications' and presented as efficacy outcomes. The evaluators collated and presented all AEs reported in the unpublished study, regardless of whether the study had presented these as efficacy outcomes.

Intraoperative complications occurred in 17 Tisseel patients and 13 suture patients ( $p=0.3429$ ) and were generally related to intraoperative bleeding (11 patients per treatment group). Two Tisseel patients and one suture patient required a postsurgical blood transfusion (one patient per group at one week and one Tisseel patient at one month). One patient per treatment group suffered an injury to epigastric vessels and one suture patient suffered an injury to the vas. The remaining intraoperative complications occurred only in Tisseel patients (small perforation of the peritoneum  $n=1$ , resection of the omentum  $n=1$ , vagal reaction  $n=1$ , testis ablation due to retained testis  $n=1$ , anaesthesia-related complication  $n=1$ ).

Postsurgery, the most frequently reported AE was fluid collection (either seroma or haematoma – not specified), which occurred in 28/158 Tisseel patients (17.7%) and 25/158 suture patients (15.8%) (no statistical analysis provided). Six events in five Tisseel patients and four events in four suture patients required puncture, and no patient required reoperation.

Bruising/ecchymosis occurred commonly (17/158 Tisseel patients [10.8%] and 19/158 suture patients [12.0%]) ( $p=0.4690$ ). Bruising/ecchymosis was generally located in the inguinal region in Tisseel patients (10/17) and in the inguinal scrotal region in suture patients (9/19). No data was provided regarding the treatment of bruising/ecchymosis.

Induration occurred in 8/158 Tisseel patients (5.1%) and 8/158 suture patients (5.1%) (no statistical analysis provided). No details were provided regarding the treatment or outcomes in these patients.

Urological complications (based on testicular examination) were reported in nine Tisseel patients (5.7%) and six suture patients (3.8%). No data were provided regarding the treatment or outcomes of these complications.

Tisseel patients were reported to have suffered more mesh infections than suture patients (3/158 [1.9%] versus 1/158 [0.63%]) (no statistical analysis provided). Three of these patients did not receive antibioprohylaxis at the intraoperative visit and no data were

provided for the remaining (Tisseel) patient. All patients received treatment which, where stated, was dicloxacillin or penicillin. Additionally, erythema was more frequently reported in Tisseel patients (5/158 [3.2%]) than in suture patients (2/158 [1.3%]) (no statistical analysis provided). No data was provided regarding the treatment of erythema.

A total of 14 Tisseel patients (8.9%) and 10 suture patients (6.4%) were readmitted to hospital at least once during the study follow up (no statistical analysis provided). Five readmissions were for AEs deemed related to treatment (Tisseel n=3, sutures n=2). Tisseel patients were readmitted for excessive pain and subcutaneous haematoma (n=1), pain caudally of the scar (n=1) and testicular pain (hydrocele) (n=1), and suture patients were readmitted for delayed wound closure (n=1) and haematoma (n=1). The authors provided a commentary on the severity of 25 reported AEs.

Most of these 25 events were considered to be of mild or moderate intensity and eight events were considered to be of severe intensity. The authors noted that events of severe intensity were not always considered to be serious. More Tisseel patients than suture patients suffered an AE of severe intensity (seven versus one). The severe events which occurred in Tisseel patients included coronary artery occlusion (n=1), gastric ulcer haemorrhage (n=1), cholelithiasis (n=1), cerebrovascular accident (n=1), pulmonary embolism (n=1), pulmonary infarction (n=1) and hip arthroplasty (n=1). The severe event which occurred in a suture patient was heart valve replacement (n=1).

Regarding postoperative pain, in both the ITT and PP analyses, at one week post surgery no significant between group differences were reported for mean VAS or the number of patients reporting 'no pain'. In the ITT analysis, at one month post surgery the mean VAS score was significantly lower in Tisseel patients (9.70 (15.94)) than in suture patients (13.08 (16.83)) (p=0.0132). This was also reflected in the PP analysis (Tisseel patients 9.71 (16.04), suture patients 13.08 (16.83)) (p=0.0138). In the ITT analysis, at one month post surgery significantly more Tisseel patients (79/152, 52.0%) than suture patients (65/157, 41.4%) reported 'no pain' (p=0.0460). The corresponding data for the PP analysis was consistent; however, no statistical analysis was provided. There was no significant between group difference for use of analgesic treatment at one week (81 Tisseel patients and 95 suture patients) (p=0.1337) or one month (13 Tisseel patients and 23 suture patients) (p=0.1080) post surgery.

In a second pivotal efficacy study, no AEs occurred during surgery for either the Tissucol or Suture group.<sup>47</sup> There were no complications from regional anaesthetic either immediately postoperatively or at 30 days following surgery and no episodes of urinary retention. A VAS pain assessment found that in the Tissucol group, 44 patients (80%) had no pain (0 on VAS), 10 (18%) had mild pain (2 on VAS) and 1 (1.8%) had moderate pain (4 on VAS). In the Suture group, 15 patients (32%) had no pain (0), 26 (47.2%) had very mild pain (2) and 14 (25.4%) had moderate pain (4).

The study noted from pain and postoperative comfort assessments at 48 hours and eight days after surgery that comfort was greater on the left side (Tissucol side) and that there was less local inflammatory reaction in this area, whereas pain was more often present on the right side and required higher doses of analgesia; however, this data was not presented in detail and statistical analyses were not performed.

In the Tissucol group, AEs occurring within the first month after surgery included seroma which resolved with suitable drainage (n=1), scrotal oedema in the surgery area which remitted at three days (n=1) and mild pain (n=1) which remitted with analgesics on the fourth day after surgery. In the Suture group, AEs occurring within the first month after surgery included a haematoma of the surgical wound (n=1) in a patient with thromboembolic prophylaxis (which required drainage), scrotal oedema and oedema of

the surgical wound which remitted in a short space of time (n=2) and mild persistent pain (n=2) or moderate pain (n=2) which ceased with analgesics.

In a pivotal efficacy study comparing Tisseel and staples, there were no intraoperative complications or hospital mortality, no major complications and no wound infections.<sup>48</sup> Daily pain scores at rest and on coughing showed no significant difference between the groups from the day of operation to postoperative day six, although less analgesic tablets were used in the Tisseel group (p=0.034). The Tisseel group had a significantly higher incidence of postoperative seroma (n=16 (17.4%); 95% CI 6.4%–28.4%) than the Staple group (n=5 (5.3%); 95% CI 0%–11.7%) (p=0.009). Urinary retention occurred in one patient (2.2%) in the Tisseel group and one patient (2.1%) in the Staple group (p=0.988). All the recorded complications resolved spontaneously without the need for surgical intervention.

In a further pivotal efficacy study, no mortality was reported and no intraoperative complications occurred in either group.<sup>49</sup> Early postoperative complications occurred in eight patients (8.1%) in the Tissucol group and in 12 patients (12.2%) in the Staple group (odds ratio 1.59 (95% CI 0.62–4.07)). In the Tissucol group, early complications reported included haematoma or seroma (n=3), orchitis (n=1), nonspecific pain (n=3) and other complications (n=1). In the Staple group, early complications included urinary tract infection (n=1), haematoma or seroma (n=4), orchitis (n=1), nonspecific pain (n=4), and other (n=2). There were no early cases of urinary retention, wound infection or neuralgia in either group. Late postoperative complications occurred in three patients (3%) in the Tissucol and nine patients (9.1%) in the Staple group (odds ratio 2.46 (95% CI 0.62–9.81)). In the Tissucol group these consisted of nonspecific pain (n=1), recurrence (n=1) (which this study considered as a safety outcome) and other (n=1) and while in the Staple group these included haematoma or seroma (n=1), orchitis or testicular problems (n=1), neuralgia (n=1), nonspecific pain (n=5) and other (n=1). There were no late cases of infection in either group. Postoperatively, the mean VAS pain score was significantly lower in the Tissucol group compared with the Staple group at one (p<0.05) and three months (p<0.001).

The remaining pivotal efficacy study compared Tissucol/Tisseel to three different staple types (Protak, EMS or EndoANCHOR).<sup>51</sup> Patients rated their pain as greatest between 24 and 72 hours postoperative and pain was rated as lowest in severity in the Tissucol group compared to the three Staple groups. At seven days, 15 days and one month, Tissucol was the only treatment which resulted in mean VAS scores of 0, with the Staple groups reporting mean VAS scores between 1 and 2. Statistical comparisons of VAS postoperative pain among the four different fixation system groups was performed using the ANOVA test. The VAS scores for 24–72 hours, 7–15 days, and one month were significantly different between the groups (p<0.05); however, it was unclear between which groups these differences lay.

No major complications or mortalities were recorded in any patient group. Total morbidity was lower in the Tissucol group (n=5, 2.2%) than in the Protak group (n=27, 14.2%) (p<0.05), the EndoANCHOR group (n=27, 13.6%) (p<0.05) and the EMS group (n=28, 14.4%) (p<0.05). Incidence of seroma was also lower in the Tissucol group (n=5, 2.2%) than the Protak group (n=12, 6.3%) (p<0.05), the EndoANCHOR group (n=15, 7.5%) (p<0.05) and the EMS group (n=13, 6.7%) (p<0.05). There were no cases of neuralgia in the Tissucol group, compared with nine (4.7%) in the Protak group (p<0.05), six (3.0%) in the EndoANCHOR group (p<0.05) and six (3.0%) in the EMS group (p<0.05). There were also no haematomas in the Tissucol group, compared with three (1.5%) in the Protak group (p>0.05), three (1.5%) in the EndoANCHOR group (p>0.05) and four (2.0%) in the EMS group (p<0.05). Persistent pain was not significantly different (p>0.05) between the

Tissucol group (n=0) and the Protak group (n=3, 1.5%), the EndoANCHOR group (n=3, 1.5%) and the EMS group (n=2, 1.0%). Two cases of urinary retention (1.0%) occurred in the EMS group only. Adverse events are summarised in Table 8.

**Table 8: Reported AEs in pivotal efficacy studies. Table continued across three pages.**

System organ class*	Adverse event	Fibrin sealant	Comparator (sutures or staples)	Total
Skin and subcutaneous disorders	Bruising/ecchymosis	17/158 (10.8%)	19/158 (12%)	36/316 (11.4%)
	Induration	8/158 (5.1%)	8/158 (5.1%)	16/316 (5.1%)
	Erythema	5/158 (3.2%)	2/158 (1.3%)	7/316 (2.2%)
	Inguinal pruriginous rash	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
<i>Unable to allocate, as each belongs to a different SOC</i>	Haematoma or seroma (not specified)	31/257 (12.1%)	30/256 (11.7%)	61/513 (11.9%)
	'Other'	2/99 (2%)	3/98 (3.1%)	5/197 (2.5%)
General disorders and administration site conditions	Excessive pain	2/158 <sup>d</sup> (1.3%)	1/158 (0.6%)	3/316 (0.9%)
	Early non-specific pain	3/99 (3%)	4/98 (4.1%)	7/197 (3.6%)
	Mild pain	1/55 (1.8%)	2/55 (3.6%)	3/110 (2.7%)
	Late/persistent non-specific pain	1/249 (0.4%)	13/548 (2.4%)	14/797 (1.8%)
	Moderate pain	0/55 (0%)	2/55 (3.6%)	2/110 (1.8%)
	Intraoperative complications	16/259 (6.2%)	13/260 (5%)	29/519 (5.6%)
	Anaesthetic complications	1/213 (0.5%)	0/55 (0%)	1/268 (0.4%)
	Oedema	3/371 (0.8%)	3/213 (1.4%)	6/584 (1.0%)
Injury, poisoning and procedural complications	Trauma elbow	0/158	1/158	1/316 (0.3%)
	Seroma	24/409 <sup>g</sup> (5.9%)	45/551 (8.2%)	69/960 (7.2%)
	Fall onto left wrist (no fracture)	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Spine injury due to motorcycle accident	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Wound dehiscence	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Reproductive system and breast disorders	Urological complications based on testicular examination	9/158 (5.7%)	6/158 (3.8%)
	Orchitis or testicular problems	2/257 <sup>a</sup> (0.8%)	2/98 (2%)	4/355 (1.1%)
	Swelling of the spermatic cord	2/158 (1.3%)	0/158 (0%)	2/316 (0.6%)
	Peyronie's disease	1/158 <sup>f</sup> (0.6%)	0/158 (0%)	1/316 (0.3%)
	Hyperplasia of prostate	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)

<b>System organ class*</b>	<b>Adverse event</b>	<b>Fibrin sealant</b>	<b>Comparator (sutures or staples)</b>	<b>Total</b>
Renal and urinary disorders	Nephritic colic	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Urinary retention	3/508 (0.6%)	5/808 (0.9%)	8/1316 (0.6%)
	Urinary tract infection	0/99 (0%)	1/98 (1%)	1/197 (0.5%)
	Dysuria	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
Vascular disorders	Deep vein thrombosis (DVT)	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Haematoma	1/363 <sup>d</sup> (0.3%)	12/663 <sup>e</sup> (1.8%)	13/1026 (1.3%)
	Sub-acute ischaemic right leg	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Anal venous thrombosis	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
Infections and infestations	Septicaemia	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Herpes zoster	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Infection	7/402 <sup>b</sup> (1.7%)	2/401 <sup>c</sup> (0.5%)	9/803 (1.1%)
Surgical and medical procedures	Hip arthroplasty	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Excision of chronic fistula after hypospadias correction	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Cataract surgery	1/158 (0.6%)	1/158 (0.6%)	2/316 (0.6%)
	Day surgery for excision of lesion from right cheek	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Thoracotomy with cardiac valve replacement	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Orthopaedic surgery (no further details)	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Delayed wound closure	0/158 (0%)	1/158 <sup>d</sup> (0.6%)	1/316 (0.3%)
	Cardiac disorders	Exacerbation of coronary heart disease	1/158 (0.6%)	0/158 (0%)
Cardiac disorders	Cardiac dysfunction	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Endocarditis	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	coronary artery occlusion	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Gastrointestinal disorders	Inguinal hernia on other (non-operated) side	1/158 (0.6%)	0/158 (0%)
Gastrointestinal disorders	Bleeding gastric ulcer	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Constipation	0/158 (0%)	2/158 (1.3%)	2/316 (0.6%)
	Acute pancreatitis	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Respiratory, thoracic and mediastinal disorders	Massive pulmonary embolisms	1/158 (0.6%)	0/158 (0%)
Respiratory distress due to pulmonary embolisms		1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
Pneumonia		0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)

System organ class*	Adverse event	Fibrin sealant	Comparator (sutures or staples)	Total
Nervous system disorders	cerebrovascular accident (CVA)	1/158 (0.6%)	1/158 (0.6%)	2/316 (0.6%)
	Loss of consciousness upon arrival at home	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Occipital right haemorrhagia	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
	Hypoaesthesia	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
	Numbness	0/158 (0%)	1/158 (0.6%)	1/316 (0.3%)
Hepatobiliary disorders	Cholecystitis	2/158 (1.3%)	0/158 (0%)	2/316 (0.6%)
	Cholecystoliasis	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)
Psychiatric disorders	Readmission to hospital for a panic attack	1/158 (0.6%)	0/158 (0%)	1/316 (0.3%)

\*as classified by the evaluators

a One patient suffered from testicular pain hydrocele which was deemed a treatment related AE.

b Four wound infections, three mesh infections.

c One wound infection, one mesh infection.

d One event was a treatment related AE.

e One was a treatment related AE.

f Relationship to treatment was 'unassessable'.

g For two events the relationship to treatment was 'unassessable'.

The most commonly reported AE in both the fibrin sealant and comparator groups was fluid collection (either haematoma or seroma; not specified). This AE had a similar rate of occurrence in each group (12.1% of Tisseel patients and 11.7% of comparator patients).

When considering seroma alone, a higher proportion of comparator patients (8.2%) than Tisseel patients (5.9%) were reported to have experienced this outcome. The second most commonly reported AE in both the fibrin sealant and comparator groups was bruising/ecchymosis, which also had a similar rate of occurrence in each group (10.8% of Tisseel patients and 12% of comparator patients). Other AEs which affected more than 5% of either treatment group included induration, intraoperative complications and urological complications based on testicular examination.

The evaluators noted that vascular, cardiac and hepatobiliary events were seen more commonly or exclusively in Tisseel patients. Expert clinical opinion indicates that generally the patients' preoperative comorbidities or medications did not appear to explain these events. Four Tisseel patients suffered a total of six unique cardiac or vascular events:

- An 84 year old patient was reported to suffer the serious AEs of cardiac dysfunction and peripheral ischaemia. This patient's comorbidities included advanced hypertension, diabetes mellitus Type 2 and a radical prostatectomy, and took cardiovascular, musculoskeletal and 'various' (undefined) medications preoperatively. These events were assessed as 'unrelated' to Tisseel.
- A 67 year old patient was reported to suffer exacerbation of coronary heart disease more than six months after receiving Tisseel. This patient was a smoker and comorbidities included post aortobifemoral surgery and coronary artery bypass graft (CABG) stenting, and cardiovascular and nervous system drugs were taken preoperatively. This event was assessed as 'unrelated' to Tisseel.

- A 61 year old patient suffered the serious AEs of coronary heart occlusions, a deep vein thrombosis (DVT), massive pulmonary embolisms and associated respiratory distress. The patient was a non-smoker and had no comorbidities, although 'various' (undefined, but not cardiac or vascular) medications were reportedly taken preoperatively. These events were assessed as 'unrelated' to Tisseel.
- A 30 year old patient suffered anal venous thrombosis, and was also readmitted to hospital for a panic attack. This patient was a smoker and had no comorbidities and was not reported to have taken any medications preoperatively. The relationship of the thrombosis to Tisseel was not assessed.

Two patients suffered a total of three hepatobiliary events:

- A 64 year old patient suffered the serious AEs of cholecystoliasis and cholecystitis more than six months after receiving Tisseel. This patient was a smoker and had no comorbidities and was not reported to have taken any medications preoperatively. These events were assessed as 'unrelated' to Tisseel.
- A 57 year old patient suffered acute cholecystitis. This patient was a smoker and had no comorbidities, although the patient was reported to have taken 'various' (undefined) medications preoperatively. The relationship of this event to Tisseel was not assessed.

Expert clinical opinion indicates that other serious AEs reported in the pivotal efficacy studies were orchitis (or testicular problems) and late/persistent non specific pain.

Although a higher proportion of comparator patients (2%) than Tisseel patients (0.8%) suffered orchitis or testicular problems, one Tisseel patient suffered hydrocele, which was deemed related to Tisseel.

#### *'Other' efficacy studies*

A total of eight 'other' efficacy studies presented safety data for Tisseel.

Two patients in the Suture group had a moderate subcutaneous serous/blood collection, and underwent reabsorption with the aid of drugs to reduce swelling.<sup>42</sup> Complications for the Tissucol group were not reported. This study indicated that Tissucol patients complained of less severe pain in the immediate postoperative period compared with patients managed using the classic technique, with a lower requirement for analgesics; however, no further data or statistical analyses were provided.

A historical control study compared fibrin sealant to sutures.<sup>43</sup> No intraoperative complications were noted in either of the groups. At Day 1, postoperative VAS pain score was  $2.1/10 \pm 1.5$  (range 0–7) in the Tisseel group. These data were absent for the sutures group because of the retrospective database. The overall immediate complication rate was 8.8% (5/57) in the fibrin sealant group versus 12.3% (7/57) in the Suture group ( $p=0.7602$ ). Immediate postoperative complications in the Tisseel group included thromboembolism (1/57), haematoma (1/57) and urinary retention (3/57), and in the Suture group they also included thromboembolism (1/57), haematoma (4/57) and urinary retention (2/57). One suture patient required reoperation due to a postoperative haematoma. While the occurrence of a haematoma was more frequent in the Suture group this difference was not statistically significant.

One retrospective case control study compared Tissucol to staples.<sup>46</sup> No serious intraoperative complications occurred in either group. Postoperative complications in the Tisseel group included two cases of seroma (2.4%), with no reports of haematoma of scrotum, trocar hernia, trocar site bleeding or 10 mm trocar site pain (measured using a



VAS). In the Staple group, complications included haematoma of scrotum (n=1; 1.14%), seroma (n=2; 2.29%), trocar hernia (n=1; 1.14%), trocar site bleeding (n=3; 4.41%) and 10 mm trocar site pain (n=4; 5.88%). The authors state that there was a significant difference between groups only in terms of 10 mm trocar site pain (p<0.05); however, trocar site bleeding also reached statistical significance (p<0.05). In each case, trocar site pain disappeared after 30 days and was attributed to fascial suturing of the site port.

One study compared Tisseel with tacks, although in this pilot study the Tisseel sample size was very small and the authors stated that the data were not appropriate for statistical analyses.<sup>50</sup> No fibrin glue related adverse effects were reported although one patient in the Tisseel group had to stay overnight due to urinary retention and later developed a one sided funicular seroma/secondary hydrocele, which required excision.

A historical control study compared Tissucol with tacks.<sup>52</sup> In the Tissucol group, there was one intraoperative bladder lesion which was managed laparoscopically and no cases of infection. There were 15 cases (6%) of seroma in the Tissucol group compared to 14 cases (5.7%) in the Staple group (p>0.05).

One study compared Tissucol to an alternative autologous fibrin sealant, Vivostat.<sup>36</sup> There was one case of seroma in the Tissucol group and no cases in the autologous fibrin group.

One retrospective study compared Tissucol to staples.<sup>53</sup> It should be noted that this study only reported complication rates as a percentage of hernias rather than as a percentage of patients (at follow up there were 173 hernias in 125 patients). There was one case of wound infection in the Tissucol group and one in the Staple group. In the Staple group there was also one case of relevant haematoma and one case of postoperative pneumonia. No clinically conspicuous seromas were documented. There was no significant difference between groups in the number of complications (one (1.2% of hernias) versus three (3.5% of hernias); p=0.621). Foreign body sensation was reported in 1/86 Tissucol hernias (1.2%) and 5/87 staple hernias (5.7%) (p=0.211).

One retrospective comparative study compared Tisseel with staples.<sup>54</sup> In the Tisseel group, eight patients (12%) had a seroma, which did not require any dedicated treatment in the majority of cases. Three patients (4.5%) had a haematoma; one of these patients had to remain on calciparin at the time of the operation and two patients (3%) had a small bowel obstruction. In this group there were no reoperations or postoperative deaths and no fever or inflammation was reported after surgery. In the Staple group, one patient (0.9%) had a wound healing problem, 12 patients (11.8%) experienced pain, eight patients (7.8%) had a haematoma, one patient (0.9%) had orchitis, one patient (0.9%) had urine retention and 10 patients (9.7%) had a seroma. Three patients in the Staple group had additional procedures but no major complications or deaths were reported in this group. There was no difference in the overall complication rates between the two groups (13/66 (20%) versus 27/102 (26%)). Commonly reported AEs in the non efficacy studies are shown in Table 9.

**Table 9: Commonly reported AEs in non-pivotal efficacy studies**

System organ class <sup>a</sup>	Adverse event	Fibrin sealant (Tissucol/ Tisseel) <sup>b</sup>	Comparator (sutures, staples or tacks)
Vascular disorders	Haematoma	4/277 (4%)	14/314 (4%)
Renal and urinary disorders	Urinary retention	4/129 (3%)	3/159 (2%)
Gastrointestinal disorders	Small bowel obstruction	2/66 (3%)	0/102 (0%)
Injury, poisoning and procedural complications	Seroma	13/524 (2%)	28/530 (5%)
	Intraoperative bladder lesion	1/250 (0.4%)	NR
Vascular disorders	Thromboembolism	1/57 (2%)	1/57 (2%)
Psychiatric disorders	Foreign body sensation	1/86 (1%)	5/87 (6%)
Infections and infestations	Infection	1/336 (0.3%)	1/87 (1%)
General disorders and administration site conditions	Postoperative pain	0/66 (0%)	12/102 (12%)
	10mm trocar site pain	0/68 (0%)	4/68 (6%)
	Trocar site bleeding	0/68 (0%)	3/68 (4%)
	Trocar hernia	0/68 (0%)	1/68 (1%)
Respiratory, thoracic and mediastinal disorders	Pneumonia	0/86 (0%)	1/87 (1%)
Skin and subcutaneous disorders	Wound healing problem	0/66 (0%)	1/102 (1%)
Reproductive system and breast disorders	Orchitis	0/66 (0%)	1/102 (1%)

a As classified by the evaluators.

b For the study by Schmidt et al (2006), only the Tissucol safety data were included in the table, and not the data for the alternative autologous fibrin sealant.

NR Not reported.

Haematoma and seroma were among the most commonly reported AEs, with similar occurrence rates between groups. While statistical analysis was not performed, the incidence of postoperative pain reported in the non pivotal efficacy studies appeared higher in the comparator group than the fibrin sealant group. Foreign body sensation was reported in more comparator patients than Tisseel patients.

Expert clinical opinion advises that small bowel obstruction, intraoperative bladder lesion and orchitis were the most serious AEs reported in the 'other' efficacy studies. One study reported two cases of small bowel obstruction only in the fibrin sealant group but the sample size was too small to draw conclusions from this. No bowel obstructions were reported in patients who received comparator treatment. Intraoperative bladder lesion occurred in one Tisseel patient and orchitis occurred in one comparator patient.

*Case series*

One study used Tissucol in 11 patients.<sup>55</sup> In this series there were no conversions to open repair or deaths, no signs of any mesh related complication and no evidence of prosthesis rejection or infection. At 10 days no patient reported severe pain; however, one patient who experienced a recurrence still reported mild pain at the three month follow up. No reports of night pain in any other patient were reported at 30 days. At follow up (mean  $14.5 \pm 1$  months) there were no reports of a feeling of stiffness or a foreign body over the mesh.

One study used Tissucol/Tisseel in 80 patients and reported no intraoperative complications.<sup>32</sup> At the seven day follow up, no sepsis, mesh rejection or other complications such as haematoma or seroma were recorded. At the six month follow up, the only complications seen were reports of moderate pain at the pubic tubercle in two patients (2.5%). At the twelve month follow up, there were no deaths and no late complications, such as scar immobility/fibrosis, neuralgia or scrotal hyperesthesia. The two patients who reported tubercle pain at six months were free of tubercle pain at 12 months.

Tissucol was used in 16 patients in a more recent case series.<sup>45</sup> Again, no intraoperative complications were reported and at the seven day follow up there were no cases of sepsis, mesh rejection or other complications such as haematomas or seroma. Fourteen patients (93.4%) reported no inguinal pain postoperatively, while two patients (13.3%) complained of slight pain related to the operation site. No adverse symptoms were reported at the one month follow up and at the three month follow up no late complications such as scar immobility/fibrosis, neuralgia or scrotal hyperaesthesia were seen. At the one year follow up all patients confirmed absence of pain.

One study used Tissucol in 40 patients.<sup>56</sup> Postoperative complications occurred in seven patients (17.5%), and included wound infection in four patients (10%) and haematoma in three patients (7.5%). The authors stated that these were minor wound problems and did not require intervention but also reported that wound infections were treated conservatively with antibiotics. Wound problems delayed the hospital discharge in two patients (5%). Seroma was not observed in this patient series. Postoperative pain occurred in two patients (5%, VAS 6 and 8). Pain was measured using the VAS (significant pain was considered with  $VAS \geq 5$ ), with postoperative pain reported in two patients (5%, VAS 6 and 8) and chronic pain one year after surgery reported in one patient (2.5%, VAS 5). During long term follow up (from one month to five years) complications occurred in two patients (5%), and included mesh infection in one patient (2.5%) and recurrence (which this study considered as a safety outcome) in one patient (2.5%). There were no postoperative deaths and all patients were alive at the follow up. Stiff abdomen was not observed.

One study used Tisseel in 1201 patients.<sup>57</sup> Postoperative pain was measured using a VAS (range 0–10), and at 24 to 48 hours after surgery the mean pain score was  $2.3 \pm 1.7$ , indicating mild pain. At this time 1021/1180 patients (86.5%) reported pain, with 232 patients (19.7%) reporting a VAS score  $>3$ . By (median) 34 day follow up, mean pain score was  $1.8 \pm 1.2$ , with 341/1185 patients (28.8%) reporting pain and 25 patients (2.1%) reporting a VAS score  $>3$ . At (median) 34 days postoperative, local complications that could be influenced by the use of fibrin sealant were recorded in 4.7% of patients overall: 3.0% of patients had haematoma, 1.4% had seroma and 0.3% (4 patients) had recurrence (which this study considered as a safety outcome). One case of infection and no cases of neuralgia at the operating site were recorded.

In another study, Tisseel was used in 38 patients.<sup>58</sup> In this series, one patient complained of postoperative pain for two weeks, which was controlled by a narcotic prescription. Follow up examination two weeks after the surgery revealed no swelling or localised abdominal pain and the patient returned to normal activities. Mean pain duration in this patient group was  $3.2 \pm 3.6$  days. Postoperative complications included orchitis (n=3), haematoma (n=2), suspected infection (n=2) (for which patients were given ciprofloxacin, and the infection resolved without further intervention), cord/canal oedema (n=15 mild, n=1 moderate), and suspected seroma (n=1) (which resolved without intervention). Three patients had chronic persistent pain.

Another study used Tisseel in 11 patients.<sup>33</sup> A seroma was observed in one patient and it resolved spontaneously within three months and required no intervention. This study verified normal urination in all patients before discharge and no other complications occurred during the observation period.

Tissucol was used in 40 patients in one study.<sup>34</sup> There were no intraoperative conversions or complications, including peritoneal or intestinal perforations. Mean pain scores, as ranked by the VAS (0–10), indicated that in spite of analgesia some patients experienced a low level of postoperative pain for the first three days following surgery which was gone by Day 7. No intra abdominal or abdominal wall haemorrhages or haematomas occurred and there were no seromas at the one or six week follow up visits. After a mean follow up of 16 (range 3 to 24) months, there were no reports of postoperative complications or deaths, no adverse gastrointestinal events (for example, nausea, vomiting, diarrhoea, abdominal distension, abdominal colic) and no reports of neuralgia.

Another study reported the use of Tissucol in 60 patients.<sup>35</sup> In this series there were no mortalities, conversions or reports of peri or postoperative complications at a mean follow up of 23.7 (range 3–39) months. There were no complications related to postoperative pain, gastrointestinal problems (nausea, vomiting, diarrhoea, abdominal bloating or colics), neuralgia, seroma, or bowel obstruction or fistula. Commonly reported AEs are summarised in Table 10.

**Table 10: Commonly reported AEs in case series**

System Organ Class <sup>a</sup>	Adverse event	Fibrin sealant (Tissucol/Tisseel)
General disorders and administration site conditions	Mild postoperative pain ( $\leq 3$ months) <sup>b</sup>	739/1305 (61%)
	Cord/canal oedema	16/38 (42%)
	Moderate/severe postoperative pain ( $\leq 3$ months) <sup>b</sup>	4/1345 (0.3%)
	Intraoperative complications	0/136 (0%)
Reproductive system and breast disorders	Orchitis	3/38 (8%)
General disorders and administrative site conditions	Chronic pain ( $> 3$ months)	6/158 (4%)
Vascular disorders	Haematoma	41/1415 (3%)
	Intra-abdominal or abdominal wall haematoma	0/40 (0%)
Injury, poisoning and procedural complications	Seroma	19/1486 (1%)
	Mesh-related complication/rejection	0/107 (0%)
Infections and infestations	Infection/sepsis	8/1426 (0.6%)
Skin and subcutaneous disorders	Scar immobility/fibrosis	0/96 (0%)
Nervous system disorders	Neuralgia	0/1397 (0%)
	Scrotal hyperesthesia	0/96 (0%)
Psychiatric disorders	Stiffness/foreign body sensation	0/51 (0%)
Surgical and medical procedures	Conversion to open repair	0/111 (0%)
Gastrointestinal disorders	Gastrointestinal problems	0/100 (0%)
	Bowel obstruction	0/60 (0%)
	Fistula	0/60 (0%)

a As classified by the evaluators.

b For one study postoperative pain outcomes were reported at two time points (two days and 34 days postoperative). The day two results are included in the table. By 34 days the number of patients reporting pain was reduced.

### **Treatment related AEs (adverse drug reactions)**

The evaluators noted that generally studies did not employ an independent outcome assessor who determined the causality of AEs. Hence, the attribution of AEs to study treatment may have been subject to bias.

Four of the five pivotal studies reported upon the outcome assessor. In two studies this was an independent surgeon (separate to the operating surgeon) and in one study the outcome assessor was a research assistant. The remaining study did not provide any details on the assessor of AEs or state that an independent outcome assessor was employed.

Only three of the eight 'other' efficacy studies reported upon the outcome assessor. In two studies the outcome assessor was an independent surgeon (separate to the operating surgeon). In the remaining study the Tisseel patients were reviewed by 'the surgeon in charge of the surgical procedures' while the comparator patients were reviewed by the same surgeon who had performed the procedure, assisted by a surgeon-in-training.

Two of the nine case series reported upon the outcome assessor. In one study an independent clinical research organisation was employed and in the second study assessments were conducted by the operating surgeon.

Only one pivotal efficacy study reported upon the relationship of AEs to study treatment.

The evaluators also noted that causality details were not provided for every AE. The authors appear to have selectively nominated the events for which this information was provided.

A total of three events in three Tisseel patients were deemed related to the treatment. All events were pain related, with additional events, and led to readmission to hospital. One patient suffered excessive pain (relieved with IV paracetamol) and a subcutaneous haematoma (no drainage performed). A second patient suffered pain caudally of the scar which was infiltrated once with local anaesthesia. The patient was not reported to subsequently suffer any pain. The third patient suffered testicular pain and hydrocele. The authors reported that no action was taken to resolve this event, which was ongoing.

Two AEs in two suture patients were deemed related to the treatment. Both events led to readmission to hospital. One patient experienced a delayed wound closure, although no further data were provided regarding the treatment or outcome of this event. Another patient who suffered haematomas and pain was treated with oral analgesics and the event was reported to have been resolved.

Three further AEs occurred in two Tisseel patients and the relationship of these events to Tisseel was deemed 'unassessable'. One patient suffered Peyronie's disease and the second patient suffered a seroma which required repetitive puncture and an additional recurrent seroma. No data were provided regarding the treatment or outcomes of these events.

One additional Tisseel patient suffered three events which were originally deemed 'unassessable' but were later revised to 'not related' to treatment. This patient suffered multiple massive bilateral pulmonary embolisms (accompanied by pulmonary hypertension, and exertional dyspnoea and DVT in the left leg with floating thrombus). This event occurred almost 12 months after the hernia repair. The patient then suffered respiratory distress due to the previous pulmonary embolisms and DVT. Finally, the patient underwent a cardiosurgery (bypass) for coronary artery occlusion.

None of the remaining four pivotal efficacy studies or the eight 'other' efficacy studies reported whether any AEs were related, or possibly related, to study treatment.

Three of the nine case series alluded to this issue. One study noted that local complications that could be influenced by the use of fibrin sealant were recorded in 4.7% of patients (3.0% haematoma; 1.4% seroma; 0.3% recurrence). The second study stated that the use of fibrin glue avoided all pain from fixation tacks and the third study stated that the use of Tisseel 'defeated the object of neuralgia'.

The Period Safety Update Report (PSUR) data noted that several events were related, or possibly related, to Tisseel. Of the 23 events that were deemed related to Tisseel, two patients suffered a haematoma (which resolved), three patients suffered complications of transplant surgery (no further details provided), one patient had no therapeutic response (which resolved) and one patient suffered a procedural complication (no further details).

In the remaining related events, Tisseel was ineffective for an unapproved indication in one patient and was ineffective in 15 other patients.

Additionally, one patient suffered ventricular failure and died. This death was deemed 'possibly related' to Tisseel.

### **Deaths and other serious adverse events**

Three of the five pivotal efficacy studies reported on deaths. One study stated that no hospital mortality occurred in either the Tisseel or Staple group<sup>48</sup>, while another stated that no mortalities occurred across any of the four prosthesis fixation groups, including Tisseel.<sup>51</sup> The remaining study reported that one Tisseel patient died six months after the hernia repair following a cerebrovascular accident (CVA).<sup>44</sup> The patient also suffered poor cardiac function, septicaemia (methicillin sensitive staphylococcus aureus (MSSA)) and occipital right haemorrhagia.

The causality of this death was assessed as unrelated to Tisseel. No deaths were reported to have occurred in suture patients.

A total of eight 'other' efficacy studies were available to inform on deaths. One study reported the death of two Tisseel patients within eight months postoperatively (both reportedly due to unrelated causes) and a third Tisseel patient within one year postoperatively but the nature of this death was not reported.<sup>54</sup> No Staple patients died. A second study reported the death of one Staple patient; however, details were not provided as to whether the death was related to the procedure.<sup>50</sup> The remaining six 'other' efficacy studies did not report whether any deaths occurred.

A total of nine case series were available to inform on patient deaths. Of these, four studies explicitly reported that no deaths had occurred, while the remaining five studies did not report on the incidence of mortality.

Instances of death in the PSUR data are discussed later in this AusPAR. Briefly, of the seven reported deaths, one was assessed as related to the product. In this case the patient underwent neurosurgery and experienced anaphylaxis, abnormal liver function tests and death. An association between Tisseel use and the reported events was ruled out by an involved surgeon but there was no specific clinical information provided to the sponsor to completely exclude Tisseel as the cause of death.

Regarding serious adverse events (SAEs), two pivotal studies reported that no 'major complication' occurred in any patient, although neither provided a definition of what constituted a major complication. An additional pivotal efficacy study did not report whether any SAEs occurred. One pivotal efficacy study stated that life threatening complications were defined before the study and were assessed for 30 days post treatment, with review by an independent Endpoints Committee to determine whether any such event was treatment related. However, no definition of life threatening complications was provided and the study made no mention of any such event occurring. The remaining pivotal efficacy study reported upon SAEs, although its authors did not define what constituted a SAE.<sup>44</sup> Seven Tisseel patients suffered a total of 10 SAEs and three suture patients suffered a total of three SAEs. As the authors of this study only provided narratives for ten of the 13 SAEs, the evaluators could not verify the treatment and resolution of several events.

Only one 'other' efficacy study provided a definition for delineation between serious and non serious adverse events.<sup>52</sup> This study defined as major complications those that led to mortality; conversion to classical laparoscopy, open surgery, or reintervention; or prolongation of hospital stay. Minor complications were defined as those that did not influence the length of postoperative hospital stay. However, this study did not report

whether any major complications occurred. One study reported that no serious intraoperative complications occurred in either treatment group. One study reported that there were no major complications in the Staple group but did not provide any reporting for the Tisseel group. The remaining five studies did not report whether any SAEs occurred.

With regards to SAEs, only one case series provided a definition of 'major complications', defined as those leading to mortality, requiring conversion to open surgery or reintervention, or those leading to prolongation of the hospital stay; the authors reported that there were no deaths or conversions to open surgical repair.<sup>55</sup> The remaining eight case series did not report on the incidence of SAEs.

The PSUR data indicated that between 1 December 2004 and 31 March 2010 a total of 221 listed and unlisted SAEs occurred. The most commonly occurred in the *Infections and Infestations System Organ Class (SOC)* (43 events).

### **Discontinuation due to adverse events**

One pivotal efficacy study reported on the rate of discontinuation due to adverse events.<sup>44</sup> A total of 20 patients (10 per treatment group) prematurely discontinued the study after randomisation. Two discontinuations were clearly due to adverse events; one Tisseel patient died after suffering a CVA and one suture patient withdrew after suffering a hernia recurrence. Of the remaining 16 discontinuations, four patients were reported to have experienced AEs and it was unclear whether these events led to discontinuation. AEs were reported in two Tisseel patients who withdrew from study (fluid collection at one month and two wound infections) and two suture patients who withdrew from study (induration of the spermatic cord and erythema). One additional Tisseel patient completed the study but the final follow up visit was delayed by several months due to AEs (massive pulmonary embolisms, respiratory distress, DVT, cardiosurgery and induration of the scar). None of the remaining four pivotal efficacy studies reported the discontinuation of study treatment and/or follow up of any patient due to AEs.

Of the eight 'other' efficacy studies, only one reported upon patient discontinuation.<sup>50</sup> This study reported difficulties in evaluating the health of one patient at the one year follow up due to comorbidities (deteriorating general health and synchronous hip joint disease). Follow up of this patient was discontinued three years postoperatively at the request of the family following further deterioration in the patients health. The authors did not report whether this discontinuation in follow up was related to the procedure or to the use of Tisseel.

None of the 'other' efficacy studies reported upon whether any patient discontinued study treatment and/or follow up due to AEs.

No case series reported the discontinuation of study treatment and/or follow up of any patient due to AEs.

### **Laboratory tests**

The evaluators considered that the monitoring of laboratory values was poor in all of the studies included in this evaluation. One pivotal efficacy study reported preoperative platelet count and prothrombin levels, and showed that there were no significant between group differences in these factors ( $p > 0.05$ ) but did not provide any postoperative measurements for comparison.<sup>44</sup> None of the pivotal or 'other' efficacy studies reported pre and postoperative data regarding serological measurements, liver and kidney function, endogenous blood clotting, or any other physiological values of potential clinical significance relating to the use of Tisseel. One case series reported preoperative chest X-ray, electrocardiogram and blood test measurements; however, no specific data was



provided for these and it was not reported whether equivalent postoperative measurements were made. Another case series recorded patients' haemostasis parameters (including prothrombin time, bleeding time and activated partial thromboplastin time) two weeks prior to treatment; however, no specific data was provided for these parameters.

### **Postmarketing experience**

Seven PSURs have been produced which cover the period between 1 December 2004 and 31 May 2010. The sponsor provided raw data from the two most recent reports (1 December 2009 to 31 May 2010 and 01 June 2009 to 30 November 2009) as well as a summary bridging report that integrated information from six PSURs and an addendum report (1 December 2009 to 31 March 2010). The reports covered the products Tissucol/Tisseel kit and duo Stim3 (licensed in 25 countries as of 31 May 2010), Tissucol/Tisseel kit and duo Stim4 (licensed in 10 countries), Fibrin Sealant VH S/D (licensed in 25 countries) and Artiss (licensed in 20 countries).

For comprehensiveness, the evaluators also searched the Manufacturer and User Facility Device Experience (MAUDE) database for any events relating to Tissucol or Tisseel.<sup>69</sup> Three entries were identified. In the first case, in July 2007 during a cranioplasty, it was reported that the Tisseel would not mix (no further details provided). Attempts were made to mix a second batch but again the Tisseel would not mix. The first batch finally mixed after one hour. The evaluators could find no evidence of this event in PSURs for this period.

In the second case, in May 2006 during an unidentified surgical procedure, Floseal, Tisseel and Coseal were used. The Tisseel and Coseal were applied with a gas driven spray device (easy spray). Following closure of the peritoneum, Tisseel was sprayed on edge of vaginal cuff. When the vaginal cuff was closed, surgeons noted that the Tisseel was 'bubbling' and wondered if this was normal but felt that this was gas trying to escape. Eighteen hours postoperatively the patient was noted to be distended. A flat plate of the abdomen was performed and pneumoperitoneum was noted which the clinician felt was related to the use of Coseal. Retroperitoneal air was also noted which the clinician felt was related to the spraying application of Tisseel. The following morning, under computed tomography (CT) guided imaging, twenty 60 cubic centimetre (cc) syringes of air were removed from abdomen and retroperitoneum. It was concluded that the pneumoperitoneum was the result of the application of Coseal and Tisseel with a spray device and not due to the presence of the products themselves. The report indicated that the surgeon required retraining regarding the use of gas driven application in closed cavities and the need to allow gas to escape from abdomen prior to closure. The clinician was reported to have agreed with this information. One case of pneumoperitoneum was reported in the Summary Bridging Report but it was unclear whether this was the same case.

In the third case, during an unidentified surgical procedure involving a left ventricular assist device in June 2009, Tisseel was used to preclot the inflow valve during pump preparation. This appears to have been an off label use of Tisseel. Leaking was found at the bottom of the inflow conduit. An attempt was made to seal the leak with additional Tisseel; however, the leaking continued. A portion of the Tisseel was removed and preclotting attempted again but leaking continued and saline was found to be dripping out of the bottom of the conduit. The surgeon decided to remove the Tisseel and use biogluce and in also placed bone wax over the biogluce. No leaking was seen after implantation. The device

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<sup>69</sup> FDA, *MAUDE - Manufacturer and User Facility Device Experience*, FDA, Silver Spring, 2011; available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm>.

manufacturer noted that the patient remains 'ongoing', although no further information was provided. The evaluators could find no evidence of this event in PSURs for this period.

The FDA website also reported that during transport the storage temperature dropped to just below the freezing point for one of the components of the kit (aprotinin). The FDA noted that this temperature deviation could lead to damage of the aprotinin vial.<sup>70</sup> The evaluators could find no evidence of this event in the PSUR for this period.

### ***Individual adverse events***

For individual AEs, the original PSURs were referred to where possible; however, as only the two most recent PSURs were provided by the sponsor, the Summary Bridging Report was used to obtain more complete data from a longer time period. From 1 December 2004 to 31 March 2010, 290 adverse reaction (AR) reports detailing 471 ARs were received worldwide by Baxter, as well as 29 medication error reports without any AR. The AR reports have been assessed as serious or non serious, and as listed or not listed. By definition, listed ARs are those whose nature, severity, specificity and outcome are consistent with the information in the safety section of the product prescribing information, while not listed ARs are those which are not consistent with the safety information provided. There were some discrepancies within the summary document; two separate tables documented the number of AR reports but the data differed between the tables. In general, the AR data provided in the summary document matched data provided in the individual PSUR of the time period 1 June 2009 to 30 November 2009, although the sponsor did indicate that the summary tabulation was generated from a dynamic database which may have been updated since the individual PSUR was produced. The most recent PSUR covered the period 1 December 2009 to 31 May 2010 and some of the recent AR reports from April and May 2010 were not incorporated into the summary document, which ended at March 2010. During this recent six month period there were five initial AR reports with Tissucol/Tisseel Stim 3 (three serious unlisted, two non serious unlisted), six with Tissucol/Tisseel Stim 4 (one serious unlisted, five non serious unlisted), nine with Fibrin Sealant VH S/D (two serious unlisted, seven non serious unlisted), one with Artiss (serious unlisted) and 23 with unspecified Fibrin Sealant (one serious listed, 22 non serious unlisted), as well as 15 medication error reports without any AR. It appears that eight of the ARs occurred too recently to be included in the summary document.

The highest proportion of symptoms reported were from the SOCs of *General Disorders and Administration Site Conditions, Injury, Poisoning and Procedural Complications and Infections and Infestations*.

For *General Disorders and Administration Site Conditions*, the most frequently reported ARs were drug ineffective (n=69) and impaired healing (n=12). Of the 12 AR reports involving impaired healing, six were assessed as related, due to a temporal association or due to an existing wound infection. Of the 69 AR reports related to drug efficacy, 56 were assessed as related, probably associated or possibly associated. This drug ineffective AR data partially overlapped with 56 reports during the review period involving a medication error, of which 29 reports involved no AR. The drug efficacy ARs listed in the PSUR of the time period 1 June 2009 to 30 November 2009 were all included in the summary document, whereas the PSUR of the time period 1 December 2009 to 31 May 2010 contained an additional six extra ARs (drug ineffective (n=4), drug effect delayed (n=1),

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<sup>70</sup> FDA, *Safety alerts for human medical products: fibrin sealant vapour heated, Tisseel VH, 2.0 mL*, FDA, Silver Spring, 2000; available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173201.htm>.

drug ineffective for unapproved indication, wrong technique in drug usage process (n=1)), all of which were possibly related to the product.

For *Injury, Poisoning and Procedural Complications* the most frequently reported ARs were seroma (n=22) and wrong technique in drug usage process (n=21). Eleven of the reports involving seroma were assessed as related, probably associated, or possibly associated. Four of these reports were for patients who developed a wound infection and seromas after mastectomy, three were for patients who developed seromas after facelifts and four were possibly associated but had a lack of case information. Of the 21 AR reports of wrong technique in drug usage process, three were serious, with two involving patients who experienced a lack of drug effect associated with inappropriate product preparation and one involving a patient with ventricular failure, inappropriate preparation of medication and lack of effect.

For *Infections and Infestations* the most frequently reported ARs were infection (n=11), hepatitis C (n=8), wound infection (n=5), and staphylococcal infection (n=4). Of the reports involving infection or hepatitis C, the majority were conservatively assessed as possibly related due to lack of information. For the five wound infection reports, four referred to the patients who developed a wound infection and seromas after mastectomy, and one was assessed as unrelated. The staphylococcal infection reports were considered unrelated.

In response to a request from several European countries, the sponsor made a commitment to monitoring the ARs of pyrexia, erythema, urticaria and chronic urticaria, aseptic meningitis following neurosurgical intervention, pseudomeningocele and all AR reports associated with drug ineffectiveness.

Seven AR reports with a fatal outcome were received during the review period 1 December 2004 to 31 March 2010 (five with Tissucol/Tisseel kit and duo Stim3 and two with Tissucol/Tisseel kit and duo Stim4). Included in these seven deaths is the one death that was reported in the recent PSUR from 1 December 2009 to 31 May 2010. All deaths were classed as unlisted. Four of these deaths were assessed as unrelated or not associated with the product. These included one death from septic shock/lung disorder/infection, one from hepatitis C, one from Proteus infection/Pseudomonas infection/wound dehiscence and one from ventricular failure/drug ineffective/wrong technique in drug usage process. Another death from extradural abscess was assessed as unlikely to be related to the product and another was not assessed due to limited information, with the patient documented as having experienced a gunshot wound and multiple abdominal trauma, coagulopathy and haemorrhage. One death was assessed as related to the product. In this case the patient underwent neurosurgery and experienced anaphylaxis, abnormal liver function tests and death. An association between Tisseel use and the reported events was ruled out by an involved surgeon but there was no specific clinical information provided to the sponsor to completely exclude Tisseel as the cause of death.

Thirty of the AR reports involved off label use of Tissucol/Tisseel kit and duo Stim3 (n=6), Tissucol/Tisseel kit and duo Stim4 (n=1), or Fibrin Sealant VH S/D (n=23). The majority of these reports resulted in drug inefficacy and were surgical procedures where only a small amount of product was applied. It was identified that using only the first few drops of the product may be the cause of the drug inefficacy as the first drops normally contain only thrombin. This led to the amendment of the product characteristics to inform users of the need to expel and discard the first few drops before product administration.

During the review period, no new safety findings were identified in a specified patient population treated with the product. Of the 147 AR reports for which patient age was

known, eight were in paediatric patients (birth–18 years) and 33 were in elderly patients (>65 years).

### **Summary**

During the review period covered in the PSURs there were several variations to the product information (PI) to clarify safety concerns. Based on the AR reports collected during the review period, no safety signals were identified for Tissucol/Tisseel kit and duo Stim3 or Stim4, Fibrin Sealant VH S/D and Artiss, although the sponsor continues to monitor identified risks such as ARs in eye disorders, AR reports of drug ineffectiveness, and ARs of pyrexia, erythema, urticaria, aseptic meningitis following neurosurgical procedures and pseudomeningocele. Based on the evaluation of cumulative AR information in the PSURs, the sponsor did not find that the reference safety information of the product needed to be changed. It should be noted, however, that the spontaneous nature of the AR reporting may underestimate true AR rates.

### **Specific safety issues of regulatory importance**

#### ***Cardiovascular safety***

In hernia repair, the comparator treatments to Tisseel are staples, sutures or tacks. The evaluators consider that these comparators would not have any consequences for cardiovascular safety or function and have therefore only extracted and presented data relating to cardiovascular safety in patients who received Tisseel during hernia repair.

In the unpublished pivotal efficacy study there was no specific reporting on the cardiovascular safety of Tisseel during hernia repair but the authors reported that several cardiovascular related AEs occurred in patients who had received Tisseel.<sup>44</sup> The authors stated that the causality of these events was 'unrelated' to study treatment. A total of three patients suffered cardiovascular events after receiving Tisseel during hernia repair. One patient experienced an exacerbation of coronary disease (angina pectoris) and was hospitalised for a coronarography. The patient had a history of cardiac disease (post aortobifemoral surgery and CABG – stenting) and that the AE took place more than six months after Tisseel was applied during hernia repair. A second patient suffered coronary artery occlusion and was required to undergo cardiosurgery (bypass). The occlusion was diagnosed almost 12 months after Tisseel was applied during hernia repair and the patient was stated to have recovered from this event without sequelae. This event was originally classified as 'not assessable' but was later revised to 'not related'. The remaining Tisseel patient suffered cardiac dysfunction. The AE took place more than six months after Tisseel was applied during hernia repair.

One 'other' efficacy study reported that one Tisseel patient suffered thromboembolism.<sup>43</sup> None of the remaining pivotal studies, 'other' efficacy studies or case series reported that any cardiovascular events took place after employing Tisseel during hernia repair.

The PSUR data revealed that a labelling variation was prompted by a retrospective observational study on 2716 patients from 1995–2000 which reported 57 fatal cases with Tissucol Duo Stim3 used in CABG surgery. The evaluators noted that a link between the use of Tisseel in CABG surgery and an increased incidence of thrombosis and subsequent morbidity and mortality was suggested. The sponsor's global pharmacovigilance Risk Management Plan (RMP) provided a retrospective statistical analysis of 2149 patient records, in which it was concluded that causality of this increased risk could not be determined and that the role of Tisseel in thrombosis could not be ruled out.

The sponsor presented one additional study which informed on the safety of Tisseel when used in CABG.<sup>59</sup> This study was not included and assessed by the evaluators as it did not assess the safety of Tisseel when used for mesh fixation during hernia repair. Briefly, this

study found an increased risk of myocardial injury or even death in coronary artery bypass grafting patients when Tissucol fibrin sealant was used intraoperatively.

The PSUR data revealed that one patient suffered ventricular failure and died. This death was deemed 'possibly related' to Tisseel.

The proposed PI indicates that Tisseel must not be applied intravascularly as this may lead to thromboembolic complications.

*The evaluators noted that expert clinical opinion suggests that extravascular application of Tisseel poses little risk of causing thrombosis when used for mesh fixation in hernia repair.*

### **Unwanted immunological events**

Although rare, some patients are hypersensitive to Tisseel. The majority of such reactions are considered non serious; however, according to the sponsor's pharmacovigilance database, three cases of death from severe anaphylactic shock have occurred following the administration of Tisseel. According to the PSUR data an additional six patients suffered anaphylactic reactions, four suffered anaphylactic shock and three demonstrated hypersensitivity.

Immunological events were not reported in the pivotal studies or case series. Two of the eight 'other' efficacy studies discussed immunological events. One study did not present any complications (fever or local inflammation) that could be related to an enhanced inflammatory process but noted that the enhanced inflammatory response induced by fibrin glue may explain the higher incidence of seromas in the Tisseel group (12% versus 9.8%).<sup>54</sup> This was echoed by another study which stated that Tisseel may stimulate a more intensive inflammatory reaction in the tissues that increase exudation and hence lead to seroma formation.<sup>48</sup>

### **Safety related to drug-drug interactions and other interactions**

No studies reported on the incidence of deleterious interactions between Tisseel and other drugs used during or after surgery. One unpublished pivotal efficacy study stated that drug-drug and drug-disease interactions were not applicable.<sup>44</sup> This same study reported that several Tisseel patients received aspirin (n=13) or heparin (n=1). Despite planning a subgroup analysis of these patients in the study protocol, the authors considered this number to be too small; hence, no analysis regarding potential interactions with these drugs and Tisseel was performed. The evaluators note that one of the patients who received aspirin suffered light intraoperative bleeding but no patients required a blood transfusion. Nine of these patients suffered AEs; however, the evaluators noted that expert clinical opinion indicates that these are unlikely to be related to an interaction between aspirin or heparin and Tisseel. Additionally, most of the AEs seen in these Tisseel patients were also reported in the suture patients who received aspirin (n=9). One additional pivotal efficacy study and one 'other' efficacy study reported on the use of low molecular weight heparin in patients undergoing hernia repair.<sup>43, 47</sup> Neither study provided any analysis regarding potential interactions with this drug and Tisseel.

In the unpublished pivotal efficacy study, a large majority of the ITT population were treated with antibiotic prophylaxis related to the surgery at the intraoperative visit (118/158 Tisseel patients and 120/158) (p=0.870).<sup>44</sup> No analysis regarding potential interactions with these drugs and Tisseel was provided.

No studies informed on whether Tisseel negatively interacts with barrier protection components present in some meshes (such as titanium, beta-glucan and collagen). Although unlikely, such an interaction cannot be excluded.

One case series reported that the dilution of Tisseel may affect its efficacy.<sup>55</sup> This study used a Surgisis mesh, which was rehydrated prior to its use. One recurrence occurred and the authors attributed this to dilution of the Tisseel as a result of mesh rehydration, leading to a loss of the Tisseel's adhesive properties. Two additional case series reported on the dilution of Tisseel in order to slow the polymerisation time and allow adequate time to fix the mesh securely. Neither study attributed any recurrences to the dilution of Tisseel.

The sponsor stated that Tisseel is susceptible to denaturation when exposed to solutions containing alcohol, iodine or heavy metals (for example, antiseptic solutions); hence care should be taken to avoid the use of these substances or remove them to the greatest extent possible prior to the application of Tisseel. No studies informed on denaturation of Tisseel when exposed to such solutions.

The sponsor suggested that there is a potential drug-device interaction (air or gas embolism and/or tissue rupture) when applying Tisseel using a spray device. Adherence to the recommended guidelines as outlined in the draft PI may reduce the risk of embolism occurring. One 'other' efficacy study reported upon embolism.<sup>43</sup> In this study the Tisseel was applied via spraying and one Tisseel patient and one suture patient suffered thromboembolism. No pivotal studies or case series reported upon the incidence of thromboembolism, although one pivotal study reported that one Tisseel patient suffered massive pulmonary embolisms after Tisseel was applied using the spray applicator.<sup>44</sup> Additionally, the PSUR data reported that one patient suffered an air embolism and one event reported on MAUDE indicated that the spray application of Tisseel led to the unwanted development of pneumoperitoneum.

### **Virology**

Tisseel is a blood derivative and therefore presents a potential risk of infection. Although a second step of viral inactivation has been included in the preparation of Tisseel, the potential for the transmission of an infectious agent (such as human immunodeficiency virus (HIV), parvovirus B19 and the prion responsible for Creutzfeldt-Jakob disease) following the use of Tisseel cannot be excluded. Despite the importance of this issue, none of the pivotal efficacy studies, 'other' efficacy studies or case series reported on serology testing or virology outcomes.

The PSUR data reported several cases of infection following the use of Tisseel. These included one case of HIV infection, two cases of hepatitis B infection and eight hepatitis C infections. Additionally, three patients were reported to have positive antibodies to hepatitis C.

There were also reported cases of meningitis, meningitis aseptic, pneumonia klebsiella, proteus infection, pseudomonas infections, staphylococcal abscess and staphylococcal infection; however, the evaluators noted that expert clinical opinion indicates that it would be unlikely that these infections were transmitted via Tisseel. Due to the amalgamated nature of the data provided in the PSURs, the evaluators could not confirm whether these events occurred in patients who received Tisseel VH/SD or in patients who received other forms of Tisseel.

The evaluators noted that the proposed PI strongly recommends that clinicians record the batch number of Tisseel used in each patient.

### **Evaluator's overall conclusions on clinical safety**

The provided studies indicated that two patients died following the use of Tisseel in hernia repair. One patient's death was assessed as 'unrelated' to Tisseel and the relation of the second patient's death was not assessed. An additional seven deaths were reported in the

PSUR data, one of which was assessed as related to Tisseel; this patient experienced anaphylaxis and abnormal liver function tests prior to death. In addition, the sponsor's pharmacovigilance database reported three cases of death from severe anaphylactic shock following the administration of Tisseel.

The evaluators noted that several severe AEs, including seroma, late/persistent non specific pain, small bowel obstruction, intraoperative bladder lesion, coronary artery disease, coronary artery occlusion, urethral repair, inguinal hernia repair, pulmonary embolism, pulmonary infarction, CVA, cholelithiasis and gastric ulcer haemorrhage were seen in patients who received Tisseel. Where assessed, none of these events were stated to have been related to Tisseel and no patients were explicitly reported to have withdrawn from trials due to AEs. In the PSUR data several SAEs occurred, most commonly in *Infections and Infestations* (43 events), *Injury, Poisoning and Procedural Complications* (34 events), *General Disorders and Administration Site Conditions* (26 events) and *Nervous System Disorders* (25 events). The evaluators noted that Tisseel is a human blood derivative and therefore presents a potential risk of infection. The PSUR data reported several cases of infection following the use of Tisseel, including cases of HIV and hepatitis B and C.

Regarding treatment related AEs, the evaluators noted that the provided studies generally did not employ an independent outcome assessor to determine causality and that these assessments may therefore have been subject to bias. Additionally, not all AEs were assessed for relationship to the study product. Twenty six events were stated to have been related to Tisseel (excessive pain/subcutaneous haematoma, pain caudally of the scar, testicular pain/hydrocele, haematoma, complications associated with transplant surgery, no therapeutic response, procedural complication, inefficacy for an unapproved indication and inefficacy). One further patient suffered ventricular failure and died and it was deemed 'possibly related' to Tisseel. The relationship of three further events to Tisseel was 'unassessable' (Peyronie's disease, seroma requiring repetitive puncture and recurrent seroma).

Generally, the remainder of reported AEs were mild or moderate in nature. The evaluators noted that the submission did not inform on any important laboratory abnormalities. In comparative studies, no AE occurred in more than 12% of either patient group. Overall, the most frequently reported AEs included fluid collection (either haematoma or seroma – not specified), haematoma, seroma, bruising/ecchymosis, induration, urological complications based on testicular examination (undefined) and postoperative pain. Where reported in comparative studies, these events generally had a similar rate of occurrence in both groups. Case series data also indicated that cord/canal oedema (42%) and orchitis (8%) occurred commonly. Orchitis was also reported upon by comparative studies which indicated that this more SAE was reported in a similar proportion across both treatment groups.

Foreign body sensation was reported in more comparator patients than Tisseel patients, although the evaluator noted that expert clinical opinion suggested that this is more likely due to the mesh than to staples, tacks or sutures. Several vascular, cardiac and hepatobiliary events occurred only in Tisseel patients; however, these did not occur sufficiently frequently to detect a pattern or trend and where assessed, were considered 'unrelated' to Tisseel. Patients affected by vascular and cardiac events generally appeared to have pre existing vascular or cardiac comorbidities but the evaluators noted that patients affected by hepatobiliary events did not have any comorbidities that would be expected to lead to these AEs. The evaluators noted that mesh infection occurred more commonly in Tisseel patients than in patients who received comparator treatment. Of the patients who were reported to have suffered this event, none were reported to have

received antibioprophyllaxis intraoperatively. The PSUR data also revealed that several *Nervous System Disorders* occurred after Tisseel application, including brain oedema, cerebral artery embolism, cerebral infarction, cerebrospinal fistula and cerebrovascular accident.

The current submission informed on some issues of potential regulatory importance. Regarding haematological toxicity, no cases of agranulocytosis or aplastic anaemia were reported, although the PSUR data revealed that two cases of serious thrombocytopenia occurred. It should be noted that the spontaneous nature of PSUR data reporting may underestimate true rates. No cases of photosensitivity, Stevens Johnson syndrome or toxic epidermal necrolysis were reported in the submission. No cases of erythema multiforme were reported; however, the current clinical submission did inform on erythema. In comparative studies erythema occurred more frequently in Tisseel patients than in suture patients and the PSUR data revealed that one case of serious erythema, three cases of non serious erythema and one case of non serious rash erythematous occurred. The sponsor's submission indicated that, in response to a request from several European countries, the sponsor made a commitment to monitoring several ARs, including erythema. The current submission did not inform on liver toxicity in patients who have received Tisseel.

The sponsor's submission informed more comprehensively on the cardiovascular safety of Tisseel. The provided studies reported that four patients suffered cardiovascular events after receiving Tisseel during hernia repair (exacerbation of coronary disease (angina pectoris), a coronary artery occlusion, thromboembolism and cardiac dysfunction). Where reported, these events were assessed as 'unrelated' to study treatment. Additionally, the sponsor's global pharmacovigilance RMP stated that the role of Tisseel in thrombosis could not be excluded. The PSUR data revealed that one patient suffered ventricular failure and died. This death was deemed 'possibly related' to Tisseel.

The evaluators noted that a link between the use of Tisseel in CABG surgery and an increased incidence of thrombosis and subsequent morbidity and mortality has been shown.<sup>59</sup>The PSUR data revealed that a labelling variation was prompted by a retrospective observational study which reported 57 fatal cases with Tissucol Duo Stim3 used in CABG surgery.

The evaluators were aware that intravascular application of Tisseel may result in thromboembolic complications and recommended strengthening the wording in the proposed PI to reflect this risk.

The evaluators noted that expert clinical opinion suggests that extravascular application of Tisseel poses little risk of causing thrombosis when used for mesh fixation in hernia repair.

The evaluators also noted the potential for unwanted immunological events when using Tisseel, including hypersensitivity to the product and anaphylactic reactions or shock. Additionally, the provided studies indicated that an enhanced inflammatory response to Tisseel may lead to seroma formation. Throughout the sponsor's submission, Tisseel appears to have been applied in a once off manner, rather than repeatedly. The evaluators noted the potential for a secondary, stronger immune response to Tisseel when it is applied more than once to a patient.

In response to a request from several European countries, the sponsor made a commitment to monitoring the ARs of pyrexia, erythema, urticaria and chronic urticaria, aseptic meningitis following neurosurgical intervention, pseudomeningocele and all AR reports associated with drug ineffectiveness. Based on the evaluation of cumulative AR information in the PSURs, the sponsor did not find that the reference safety information of



the product needed to be changed. It should be noted, however, that the spontaneous nature of the AR reporting may underestimate true AR rates.

The evaluators noted that the method of application of Tisseel may have associated safety issues. The submission did not inform on the maximum thickness of which Tisseel may be safely applied. Application via a spraying device remains a valid safety concern and the evaluators noted that this issue has been addressed in the draft PI.

The evaluators noted that expert clinical opinion indicates that Australian surgeons are very likely to use Tisseel in patients and indications beyond those approved by the TGA. This opinion is reflected by the PSUR and MAUDE data which reveal that Tisseel has been used in an off label manner in at least 30 instances. However, as these data are reported voluntarily and the population is of uncertain size, the frequency of off label use may be much higher. International PI documents suggest that the safety of Tisseel when applied to other tissue types (neural, nasal mucosa, ophthalmic, neural) is unclear.

The evaluators noted that the safety of Tisseel when used in children and pregnant or breastfeeding women remains unclear. Additionally, the provided studies generally excluded patients who were deemed unsuitable to receive the surgical technique of interest or those with contraindications to surgery or general anaesthesia (severe cardiopulmonary disorders, ASA class IV–V, portal hypertension, bowel obstruction/strangulation/perforation, peritonitis, local/systemic infection). No studied patients were aged less than 18 years and very few were aged over 80 years. No other special risk patients were studied. Patients who required concomitant abdominal surgery or who were enrolled in another trial were generally excluded. The safety of Tisseel in these patient populations is unclear. Additionally, the safety of Tisseel when used in non abdominal wall hernias remains unclear. As no special risk patients were included, no dose adjustment recommendations for these groups may be made.

The evaluators presented the following areas of disagreement with the sponsor's *Clinical Overview*.

The sponsor stated that the incidence of postoperative haematoma or seroma, when Tisseel was used compared with conventional methods, was decreased in six studies, comparable in six studies and increased in one study. The evaluators treated this data in an aggregated manner and noted that these outcomes were generally reported in a similar proportion across both treatment groups.

The sponsor stated that the PSUR did not reveal any immunogenic reactions or viral transmissions. The evaluators identified several instances of immunogenic reactions and viral transmissions. Due to the aggregated nature of these data the evaluators were unable to verify whether these events occurred in patients who received Tisseel VH/SD or in patients who received other forms of Tisseel.

The sponsor stated that only one study reported AEs other than infection. The evaluators considered that the vast majority of the 22 eligible safety studies reported safety outcomes. The evaluators agreed that the unpublished pivotal efficacy study provided the most detailed reporting of AEs.

The sponsor stated that other complications of the procedure were considered to be efficacy outcomes. The evaluators considered this assignment to be incorrect.

The evaluators considered that the sponsor has failed to detail all reported AEs.

The sponsor stated that one study reported upon death. The evaluators identified eight studies that reported on this outcome and suggested that the sponsor amends this paragraph.

### **Additional studies providing safety evidence**

The sponsor provided two additional randomised controlled trial (RCTs) published following the original application (Bittner et al 2011; Eriksen et al 2011).<sup>71,72</sup> Descriptions of these studies and safety issues identified within these publications are presented below.

#### ***Bittner et al (2011)***<sup>71</sup>

*Bittner et al (2011)* performed a randomised controlled trial comparing four meshes in patients with either primary or recurrent inguinal or femoral hernia undergoing laparoscopic TAPP. During the study period, 2,754 inguinal and femoral hernia repairs were performed, however only 600 were eligible for randomisation intraoperatively to the heavyweight, medium weight, light weight or titanium lightweight mesh groups (150 per group). Baseline characteristics were similar between groups with regards to sex ratio, age and BMI.

To be eligible for inclusion, patients required a reducible primary or recurrent inguinal or femoral hernia, were aged over 30 years and had a hernia opening of between 3-5 cm. Exclusion criteria consisted of a defect size less than 3 cm or greater than 5 cm, irreducible and scrotal hernia, emergency case, trainee operation (less than 50 self performed TAPPs), patients with inguinal neuralgia or inability to understand the study design.

All procedures were carried out under general anaesthetic and all meshes were fixed with 2 mL of Tisseel; however the specific method of application was not reported. Patients received thromboembolic prophylaxis with low molecular weight heparin and antibiotic prophylaxis immediately before surgery.

No differences were observed in early or late postoperative surgical complications between meshes, with incidence ranging from 0.66% to 3.3%. These consisted primarily of trocar hernias (n=4), lesion of the cutaneous femoral nerve (n=3), haematoma (n=1), lesion of the genital branch of the genitofemoral nerve (n=1) and persistent seroma (n=1). The authors stated that fibrin sealant was well tolerated and none of the postoperative events were deemed to be related to its use. In a subsection immediately preceding the discussion, the authors stated that there was no significant difference in detectable seroma formation between the four groups, with incidence ranging from 16% (titanised lightweight mesh ;TLW) to 26% (polypropylene mesh ;MW). These values are significantly higher than those presented within the clinical evaluation report, which presents values ranging from 0% to 12% seroma formation.

#### ***Eriksen et al (2011)***<sup>72</sup>

Forty of 111 eligible patients (20 per group) were included in the study following the application of exclusion criteria. Patient demographics were similar between groups, with the exception of mean age (45 versus 59 years in the tack and fibrin sealant groups, respectively. p=0.014). Inclusion criteria consisted of patients with symptomatic umbilical hernia with a diameter of 1.5 – 5 cm; age 18-85 years, Danish speaking and ASA Grade I-

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<sup>71</sup> Bittner R, Leibl BJ, Kraft B, Schwarz J. One-year results of a prospective, randomised clinical trial comparing four meshes in laparoscopic inguinal hernia repair (TAPP). *Hernia* 2011; 15: 503-10.

<sup>72</sup> Eriksen JR, Bisgaard T, Assaadzadeh S, Nannestad Jorgensen L, Rosenberg J. Randomized clinical trial of fibrin sealant versus titanium tacks for mesh fixation in laparoscopic umbilical hernia repair. *British Journal of Surgery* 2011; 98: 1537-1545.

III<sup>73</sup>. Exclusion criteria consisted of patients with previous laparoscopic umbilical herniotomy or open operation with mesh, strangulated hernia, previous or current use of opioid medication, expected poor compliance (such as psychiatric disorder), chronic liver disease, known immune deficiency including current systemic steroid use or other immunosuppressive treatment, pregnancy, medical conditions contraindicating general anaesthesia, simultaneous operation for another hernia, or hernia defect larger than 6 cm.

All patients underwent general anaesthesia and received 1.5 g cefuroxime prior to surgery. One 12 cm round Parietex Composite mesh was used for all operations. For 8mL of fibrin glue was used per hernia; however, the authors replaced the 500 unit/mL thrombin with 4 unit/mL thrombin to delay coagulation (that is, the same thrombin concentration as Artiss). The fibrin glue was applied using a DuploSpray MIS applicator without the spray function.

One patient allocated to the Tack group was excluded during the operation due to the large hernia diameter (>7 cm) and one patient allocated to the fibrin sealant group did not complete the postoperative questionnaires and therefore was lost to follow up. Two patients (10%) in the fibrin sealant group required tack fixation owing to technical failure of the sealant; however these two patients were included in the fibrin sealant ITT population for subsequent analyses, resulting in 19 patients per group.

The primary safety outcome of interest was acute postoperative pain on Days 0-2 after surgery, with Day 0 being the day of surgery. Pain was measured using both a VAS scale ranging from 0 mm (no pain) to 100 mm (worst pain imaginable) and a verbal rating scale (VRS; 0, no pain; 1, slight pain; 2, moderate pain; 3, severe pain).

Mean pain was considerably lower in the fibrin sealant group compared to the Tack group when measured at Days 0-2, with scores of 47 (6-91) and 19 (3-74) for tacks and fibrin glue while at rest, and scores of 60 (18-96) and 38 (6-98) for tacks and fibrin glue during activity, respectively.

Postoperative complications observed within 30 days of surgery were similar between groups and were not significantly different from the types of complications observed in those studies included within the report (Table 11); however the rate of seroma formation was exceedingly high. That being said, seroma formation was also high in the Tack group and is not specific to fibrin glue patients, suggesting that it most likely resulted from the surgeons' protocol and was not inherent to fibrin glue only.

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<sup>73</sup> The American Society of Anesthesiologists (ASA) physical status classification system is a system for assessing the fitness of patients before surgery. In 1963 the ASA adopted the five category physical status classification system; a sixth category was later added. These are:

- I. A normal healthy patient.
- II. A patient with mild systemic disease.
- III. A patient with severe systemic disease.
- IV. A patient with severe systemic disease that is a constant threat to life.
- V. A moribund patient who is not expected to survive without the operation.
- VI. A declared brain-dead patient whose organs are being removed for donor purposes.

**Table 11: Complications within 30 days postoperatively for Eriksen et al (2011)**

Complication	Tack fixation (n=19)	Fibrin glue (n=19)
Seroma	7 (37%)	6 (32%)
Haematoma	3 (16%)	4 (21%)
Superficial infection	1 (5%)	2 (10%)
Skin erythema	0	1 (5%)
Readmission	2 (10%)	1 (5%)
Recurrence	0	0

### List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

#### Clinical questions

*Generally, the formulations of Tisseel used throughout the sponsor's submission were not specified. Does the sponsor have any evidence, published or otherwise, regarding the use of the VH/SD formulation for mesh fixation in hernia repair?*

The sponsor stated that as Tisseel VH/SD has only recently been launched, there is currently no evidence regarding the use of Tisseel for mesh fixation in hernia repair. The sponsor highlighted an ongoing trial in which no AEs have yet been reported, however no data has been provided to support this statement.

Tisseel VH/SD differs from the previous generation of fibrin sealant (Tisseel Duo 500) due to the inclusion of an additional solvent/detergent viral inactivation step, reduction in Factor XIII concentration and modification of manufacturing processes. The evaluators could find no evidence to suggest that these modifications have reduced the safety or efficacy of Tisseel VH/SD when used for mesh fixation in hernia repair compared to Tisseel Duo 500.

*Does the sponsor have any data to inform on the maximum size of the area to be covered when applying Tisseel via spraying, as per the USA PI?*

The sponsor claimed that the use of a spray set allows a trained user to cover with 2 mL of final product a surface of at least 100 cm<sup>2</sup>. The sponsor Burn Study 520001 using Artiss (a low thrombin concentration fibrin glue), previously submitted to the TGA under a different application, was used to provide evidence in support of this claim. Unfortunately, this study was not provided in this application and subsequently cannot be used to inform on this issue.

*The sponsor advised that a thin layer of Tisseel should be applied. Can the sponsor provide parameters to indicate excessive application, such as a maximum glue height/thickness (mm) or other visual indicators?*

The sponsor stated that upon polymerisation, Tisseel VH/SD becomes opaque/whitish. The intensity of colour is claimed to provide the experienced user with an indication regarding the thickness of the clot. The sponsor proposed a five step approach focussed on providing practical education to clinicians regarding use of Tisseel for hernia operations; however, advice on what constitutes sufficient or excessive application was not explicitly stated as being included in this education program.

The sponsor provided several visual cues which may be indicators of excessive application of product. These consist of an intensive white colour of the clot, the impression that the clot is like a 'sugar head' (no further details provided), and when the product is 'bulging out'. The sponsor stated that, based upon the whitish colour, excessive product can be cautiously removed; however, no details or guidance were provided regarding this process.

*The sponsor stated that following Tisseel application, the mesh should be held in place for the duration of the polymerisation reaction (at least three to five minutes). Can the sponsor provide visual cues or measures for the success of the reaction?*

The sponsor stated that following application, Tisseel becomes first slightly opaque and then develops a whitish colour, providing a visual cue that a reaction between fibrinogen and thrombin is occurring. The sponsor acknowledged that this is difficult to visualise if Tisseel is applied under the mesh or is applied to a non porous mesh. To confirm when sufficient strength has been achieved, the clinician should remove the instrument holding the mesh in place to observe any movement of the mesh. When no movement of the mesh is seen, the clot was stated to have sufficient strength. The sponsor indicated that this may take up to 5 minutes. Within the Australian PI, the sponsor recommends holding the sealed parts (of the mesh) in the desired position for at least 3-5 minutes.

Although the change in colour, from opaque to 'whitish' can be used to inform the clinician that sufficient polymerisation has occurred, such knowledge is only available to clinicians who are familiar with the product. The sponsor did not provide any data specifying what stage of clot formation represents sufficient strength to hold the mesh in place.

*In the five pivotal efficacy studies, between 1 and 4 mL of fibrin sealant was used per hernia. None of the studies provided a rationale for the quantity of Tisseel used. Could the sponsor provide any further data to inform on the optimal dose of Tisseel?*

The sponsor referred to the Austrian Summary of Product Characteristic (SPC) document and stated that 1 mL of Tisseel VH/SD solution plus 1 mL of thrombin solution is suitable for an area of at least 10 cm<sup>2</sup>. The sponsor stated that the value derived within the Austrian SPC document applies to the dripping method of application; however, this is not specified in the Austrian SPC document. The US Product Information (PI) states that 2 mL of Tisseel is sufficient to seal an area of no more than 100 cm<sup>2</sup> using compressed gas. The US PI contradicts the Austrian SPC, as it states that the maximum size of the area to be sealed using a cannula is 8 cm<sup>2</sup> for 2 mL of Tisseel. The sponsor stated that as a result of these documents, the amount of Tisseel used within the unpublished pivotal efficacy study was primarily dependent on the size of the mesh and that the investigators used between 0.5 and 2 mL of Tisseel VHSD solution per hernia site (between 1 and 4ml for bilateral hernia).

*The authors of the unpublished pivotal efficacy study stated that an analysis to show equivalence was not applicable and the evaluators have therefore assumed that this was not an equivalence study. However, the authors did not explicitly state that the study was designed to demonstrate superiority or non inferiority. Could the sponsor advise the study design of the unpublished clinical efficacy study (equivalence, non inferiority, superiority)? If this is a noninferiority study, please provide the non inferiority margin.*

The sponsor stated that the unpublished pivotal efficacy study was a superiority study. Such a study is based on the assumption that there is a statistical difference between the incidence of a specific outcome between the investigational and comparator treatments. The sponsor provided a point estimate of 12.5% and 25% (two fold increase) of chronic pain, numbness, or groin discomfort at 12 months following hernia repair using Tisseel and sutures, respectively. The sponsor assumed a power of 80% and a two-sided test

significance level of 5%, giving a total sample size of 298 patients. Considering a 10% dropout rate, this increased the required number of patients to 328, of which 315 were evaluated in total.

As noted in the original report, the authors did not provide a citation for the assumption of 10% chronic pain. A recent Cochrane review (McCormack et al 2008) demonstrated a 16.12% to 23.14% incidence of chronic pain following open repair of inguinal hernia, suggesting that the unpublished pivotal efficacy study may have been underpowered.<sup>63</sup>

*The evaluators note that, generally, the length of follow up in the clinical efficacy studies was ≤12 months, which may be insufficient for evaluating hernia recurrence. Does the sponsor have access to any additional studies that employed a longer follow up?*

The sponsor highlighted five studies which provide data on follow up periods of greater than 12 months.

Two of the suggested studies were not included in the original application and subsequently could not be used to inform on this issue. The evaluators confirmed the incidence of one hernia recurrence (out of 40 patients) at 18 months in the study by Canziani (2009).<sup>56</sup> Safety data from this study was included in the original evaluation report; however, this study did not fulfil the efficacy inclusion criteria and thus the recurrence outcome was omitted from analysis. The evaluators confirmed that no recurrences were observed in the study by Lau et al (2005)<sup>48</sup> at a median follow up of 1.2 years and that a non statistically significant higher incidence of recurrences had occurred in the Staple group compared to the Tisseel group in the study by Schwab et al (2006)<sup>53</sup> at the mean 15.3 month follow up. However, these data were included in the original evaluation report and thus do not present any additional evidence. The evaluators concluded that no additional evidence has been provided informing on the long term incidence of hernia recurrence.

*Regarding the unpublished pivotal efficacy study, the evaluators could not identify any evidence indicating that the VAS has been validated for measuring numbness or groin discomfort after hernia repair. Can the sponsor provide any evidence that VAS has been validated for this purpose?*

The sponsor stated that the VAS tool used to measure numbness and groin discomfort following hernia repair had not been validated. Having used this VAS tool for chronic pain assessment and having combined all three outcomes (chronic pain, numbness and groin discomfort) as a composite endpoint, the sponsor stated that it 'appeared logical' to use the same VAS tool to measure all three components of the endpoint.

The evaluators considered it inappropriate to use a non validated tool to measure numbness and groin discomfort, which were two of the three outcomes used in determining whether Tisseel is superior to sutures in the unpublished efficacy study.

*Is the sponsor able to provide any data to inform on the susceptibility of Tisseel to denaturation when exposed to solutions containing alcohol, iodine or heavy metals?*

The sponsor stated that no specific investigations addressing the incompatibility of Tisseel with solutions containing alcohol, iodine or heavy metals have been performed and thus no data explicitly confirming this statement are available. The sponsor stated that it is common understanding that these substances cause denaturation of proteins. The evaluators confirmed that a precautionary statement has been included in the PI in order to avoid the exposure of Tisseel to these substances.

*Is the sponsor able to provide any data to inform on the adhesive qualities of Tisseel when diluted or when applied to a mesh which has been rehydrated with water?*

The sponsor stated that the application of Tisseel to rehydrated meshes is not expected to lead to a dilution of Tisseel

The sponsor did not provide evidence to support this claim. In addition, the sponsor failed to provide comment on whether dilution of Tisseel would affect its adhesive qualities.

*The evaluators note that a wide variety of coatings are available, including titanium, beta glucan, omega-3 and collagen<sup>74,75</sup>. Could the sponsor provide any data to inform on the efficacy of Tisseel when used with various mesh coatings? Can these coatings decrease Tisseel's ability to penetrate the mesh?*

The sponsor provided evidence regarding the efficacy of Tisseel when used with various mesh coatings and whether they decrease Tisseel's ability to penetrate the mesh. However, many of the studies used as support were not provided in the original application and thus could not be used to inform on this issue.

The evaluators confirmed that one study reported a 2.3% recurrence rate at a mean follow up of 15.3 months (Schwab et al 2006).<sup>53</sup> However, this was the rate observed for Tisseel patients only, of which there were 86 hernias (not the 133 patients with 186 hernias as reported in the sponsor's response). Olmi and colleagues laparoscopically repaired 61 inguinal hernias (Olmi et al 2007c) and 40 ventral hernias (Olmi et al 2007b) using the Parietex composite mesh (polyester mesh coated with porcine collagen, PEG and glycerol), with no recurrences observed at mean follow up of 23.7 months (Olmi et al 2007c) and 16 months (Olmi et al 2007b).<sup>34,35</sup> The evaluators had not included the Olmi et al (2007b) study in the efficacy section of the clinical evaluation report as it was not clearly used to affix mesh during hernia repair. Petter-Puchner et al (2005) demonstrated high bursting pressures and pulling forces in a rat model using fibrin glue and Ti-mesh and Vypro (polypropylene coated with polyglactin 910), leading to what the authors call 'convincing results' in terms of tissue integration and biomechanical qualities.<sup>11</sup> The evaluators assumed that this study has been evaluated as part of the nonclinical evaluation as it was not performed in humans.

The sponsor stated that an associated pilot study demonstrated that acute fixation was not achieved with C-Qur (polypropylene-coated with Omega 3 fatty acid) or Dualmesh (pure, non-porous ePTFE mesh). However, details of the study were not provided. The sponsor stated that to their knowledge, there are no published data regarding the use of beta glucan-coated meshes fixed with Tisseel in a nonclinical or clinical setting.

The evaluators considered this issue to be significant and recommended that the sponsor includes a statement within the Australian PI.

*Non-stick meshes are designed to protect the viscera from adhering to the polymeric prosthetic long enough for the body to cover the mesh with a mesothelial layer. Could the sponsor provide any data to inform on the efficacy of Tisseel when used in conjunction with non-stick meshes?*

The sponsor did not provide any additional evidence regarding the efficacy of Tisseel when used on non-stick meshes, instead referring to the answer provided for the previous question. The sponsor noted that C-Qur mesh is non-stick and that acute fixation using Tisseel was not achieved using this mesh in an unidentified, associated pilot study.

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<sup>74</sup> Champault G, Barrat C. Inguinal hernia repair with beta glucan-coated mesh: results at two-year follow up. *Hernia* 2005; 9: 125-30.

<sup>75</sup> Earle D, Romanelli J. Prosthetic materials for hernia: what's new. *Contemp Surg* 2007; 63: 63-9.

The evaluators considered this issue to be significant and recommended that the sponsor includes a statement within the Australian PI.

*The PI notes that the sealer protein and thrombin solutions may be denatured following contact with solutions containing heavy metals. Has the sponsor conducted any investigations into whether any metallic coated meshes may denature the sealer protein and thrombin solutions?*

The sponsor stated that the sole metallic coated mesh is the Ti-Mesh. This is covered in a microscopic layer of titanium and is not known to provoke any denaturation of fibrin. The sponsor cited two studies in which Tisseel was applied to Ti-Mesh. In the first (Petter-Puchner et al 2005), the sponsor claims that the authors had conducted a successful preclinical trial with this kind of mesh.<sup>11</sup> The evaluators confirm that no failure in mechanical tests (tensile and burst strength) occurred in sealed meshes in this study. The second study was not submitted with the original application and thus could be used to inform on this issue.

### **Safety**

*The evaluators noted the lack of data on the cumulative effect of applying Tisseel to more than one location during surgery or when applied over the course of several surgeries. Does the sponsor have any evidence, published or otherwise, to inform on this issue?*

The sponsor acknowledged the likelihood that Tisseel will be applied to more than one location during the same surgery. The sponsor stated that neither clinical studies nor postmarketing surveillance data demonstrate an accumulative effect when using Tisseel and that such an event is unlikely due to the quick rate of resorption of Tisseel (10-14 days) following application. The sponsor stated that in those instances where the application of additional Tisseel is required prior to full resorption, residues of Tisseel have to be removed before new application at the same site. It is not recommended to apply Tisseel on already polymerised Tisseel if adherence is required.

The sponsor did not provide any additional evidence to support the rate of Tisseel resorption. The evaluators confirmed the presence of a statement within the Australian PI.

*The evaluators noted the lack of data to inform on the likelihood and extent of a secondary immune response to Tisseel when applied to more than one location during surgery or when applied over the course of several surgeries. Does the sponsor have any evidence, published or otherwise, to inform on this issue?*

The sponsor stated that immune response reactions are 'not really' dependent on the number of locations to which Tisseel is applied during the same surgery but rather on repeat application over time. The sponsor cited one study regarding the treatment of recalcitrant venous leg ulcers; however, this study was not included in the original application and thus could not be used to inform on this issue.

No evidence was provided to support the statement that immune response reactions are 'not really' dependent on the number of locations to which Tisseel is applied. The evaluators noted that a statement has been included in the Australian PI.

*The submission indicated that several patients have suffered anaphylactic reactions and hypersensitivity after receiving Tisseel. Does the sponsor have any evidence, published or otherwise, to further inform on the immune response to Tisseel?*

The sponsor stated that the most comprehensive evidence regarding immunogenic potential of systemically or topically applied aprotinin is provided in three studies by Scheule et al (1998; 1999; 2000) in which no patients experienced an allergic reaction. However, none of these studies were included in the original application and thus could



not be used to inform on this issue. Furthermore, the absence of anaphylactic reactions within these three studies does not inform on the incidence of anaphylactic reactions in every case of Tisseel use.

The evaluators wished to draw attention to the sponsor's pharmacovigilance database in which three cases of death occurred from severe anaphylactic shock following the administration of Tisseel. Additionally, the provided PSUR bridging data (1 December 2004 to 31 March 2010) reveals that an additional six patients suffered anaphylactic reactions, four suffered anaphylactic shock and three demonstrated hypersensitivity.

*The submission lacks data surrounding virus transmission and antibody formation following the administration of Tisseel. Does the sponsor have any evidence, published or otherwise, to inform on this issue?*

The sponsor stated that 'in more than 30 years of commercialization of Baxter's fibrin sealants, no transmission of hepatitis A, B or C nor HIV has been confirmed'. The sponsor cited a further two studies (total n=268) in which no seroconversion was confirmed. These studies were not included in the original application and thus could not be used to inform on this issue.

The evaluators noted that two cases of hepatitis B and one case of HIV were reported in the sponsor's PSUR bridging data (1 December 2004 to 31 March 2010). No further details were provided regarding these cases. In addition, eight cases of hepatitis C were reported in the sponsor's PSUR bridging data (1 December 2004 to 31 March 2010). Transmission was assessed as 'unrelated' or 'unlikely associated' in five of these reports; however the remaining three reports were conservatively assessed as 'related' given the lack of information provided.

*The sponsor's search strategy suggests that Tisseel has been considered for an additional indication (sealant/gluing use in dural sealing). Has a submission for this indication been considered by the TGA or by any international bodies?*

The sponsor confirmed that Tisseel has not been submitted to the TGA for the purpose of obtaining the indication of sealant/gluing use in dural sealing. The sponsor stated that the clinical study report of an exploratory Phase II study has been submitted to the FDA and countries in Europe but that this is for reference only.

*International PI documents suggest that the safety of Tisseel when applied to neural, nasal mucosa, ophthalmic and neural tissues is unclear. Although Tisseel is unlikely to be applied to these tissue types during hernia repair, the evaluators anticipate that clinicians will use Tisseel in an off label manner. Is the sponsor aware of any specific safety issues associated with applying Tisseel to any non hernia related tissues or locations?*

The sponsor presented three publications which describe the use of Tisseel in neural tissues, six studies in ophthalmic tissues and four studies in nasal mucosa. None of these studies were submitted with the original application and thus they could not be used to inform on this issue.

The sponsor stated that all reports from spontaneous, regulatory, clinical and/or literature sources involving off label use will be entered into the Baxter Pharmacovigilance Database, to be discussed in PSURs on an ongoing basis.

The evaluators confirmed that the Australian PI contains information pertaining to the risks involved with thromboembolic events following intravascular application, risk of compressive symptoms when applied in closed spaces and possible increased risk of allergic reaction when applying to mucosal surfaces, particularly the nasal mucosa.

*The submission indicated that several nervous system disorders occurred after Tisseel application, including brain oedema, cerebral artery embolism, cerebral infarction, cerebrospinal fistula and cerebrovascular accident. Does the sponsor have any evidence, published or otherwise, to inform on any nervous system-related safety issues that may be associated with Tisseel?*

The sponsor acknowledged that there is a reasonable possibility of a causal relationship between intravascular application of Tisseel and thromboembolic complications. The sponsor claims that three spontaneous case reports were identified in Baxter's Adverse Event Reporting System database as postmarketing reports up to 27 July 2009 (cerebral artery embolism, cerebral infarction, cerebrovascular accident).

The evaluators confirmed that these three cases were reported in the PSUR report provided (1 June 2009 to 30 Nov 2009); however, two additional cases of brain oedema were also reported in this document. The sponsor stated that when using fibrin sealants in confined bodily spaces, the risk of compressive complications should be taken into account. A statement to this effect is included in the Australian PI. The sponsor provided additional evidence in the form of an internal study; however, this study was not included in the original application and thus could not be used to inform on this issue.

*The evaluators noted that mesh infection appeared to occur more commonly in Tisseel patients than in patients who received comparator mesh fixation methods. Does the sponsor have any evidence, published or otherwise, to further inform on this issue?*

The sponsor cited 13 studies as providing evidence to inform on this issue used in the TGA safety assessment; however the evaluators identified and incorporated 22 studies in the safety assessment. As the sponsor failed to provide the study details, the evaluators were unable to identify which 13 studies the sponsor referred to. The sponsor identified one postmarketing case report regarding infection in Baxter's Pharmacovigilance Database (12 November 1991 to 12 August 2011), when cross-referencing this with the MedDRA System SOC of *Infections and Infestations and Investigations*. This case involved a patient with hepatitis C in which Vicryl mesh was used to wrap the spleen. The reporters ruled out Tisseel as the source of infection; however no justification for this conclusion was provided.

The evaluators identified eleven cases of infection within the PSUR summary bridging data (December 2004 to 31 March 2010) which were classified as being 'related' or 'possibly associated' to the use of Tisseel. One additional case of bacterial infection was identified in the PSUR from 1 December 2009 to 31 May 2010 which was assessed as being possibly associated with Tisseel due to the lack of information.

*In the unpublished pivotal efficacy study, outcomes for 'urological complications (based on testicular examination)' were reported. No details were provided regarding the nature of these complications and it was unclear how these events were recorded and defined. Could the sponsor provide a clear definition of what was considered a 'urological complication based on testicular examination'?*

The sponsor stated that investigators assessed urological complications based on testicular examination 'like' testicular inflammation (orchitis), testicular atrophy and testicular necrosis. It was unclear whether there were any further complications considered. This outcome was assessed by evaluating the location of the testicle (normal or high) and the volume (normal, larger, smaller) with regards to the side of the operated hernia. The sponsor claimed that there was no significant difference between these groups.

The evaluators found a discrepancy with this definition through analysis of the sponsor's unpublished pivotal efficacy study assessed in this report. The majority of urological complications reported (20/31 Tisseel and 22/28 sutures) were accompanied by no change in testicular location and/or volume. The evaluators also assessed the individual patient data provided by the sponsor in the unpublished pivotal efficacy study. There was no statistical difference between Tisseel and sutures patients with regards to the incidence of urological complications; however, there was a measurable difference in testicular location and size. The evaluators noted that expert clinical input indicates that this may present a safety issue, as higher testicles may be more prone to being drawn up into the inguinal canal.

*In the unpublished pivotal efficacy study, preoperative platelet count (mm<sup>3</sup>) and prothrombin levels (%) were reported but no postoperative measurements were provided. Could the sponsor provide the corresponding postoperative measurements to permit comparison?*

The sponsor confirmed that platelet count and prothrombin levels were not recorded postoperatively. The sponsor stated that such measurements were made so as to detect any patient with impaired coagulation that could have been linked with bleeding complications.

The evaluators acknowledged the importance of ensuring homogeneity between treatment groups regarding the possibility of bleeding complications (as determined through platelet count and prothrombin levels); however the evaluators considered it useful to report postoperative values to assist in determining the incidence of thrombocytopenia and other related bleeding complications.

*The evaluators identified several adverse events in the MAUDE database which were not included in the PSUR data. Is the sponsor aware of any additional events which have not been presented in the dossier?*

The sponsor reviewed three cases of adverse events as listed in the MAUDE database. The evaluators confirmed the sponsor's synopsis of the first report, in that the report presented a case of the product not mixing properly and did not constitute a safety related adverse event. The evaluators confirmed the synopsis of the second case in that the adverse event was related to the use of a device (Tissomat) in conjunction with a comparator product and was not directly related to the use of Tisseel. The third report of an adverse reaction using Tisseel was included in the PSUR reporting period 1 December 2008 to 30 May 2009. The sponsor stated that all cases of adverse events reported to Baxter's pharmacovigilance department would be presented within the PSUR as per regulations and requirements.

*The evaluators remained concerned by the cardiovascular safety profile of Tisseel. Does the sponsor have access to any additional data, published or otherwise, surrounding the safety of Tisseel when applied directly to cardiac tissue (such as during CABG)?*

The sponsor stated that: "there are no substantiated safety issues regarding the use of Tisseel on cardiac tissue"; however the sponsor provided a study that identified a statistical association between the use of fibrin sealant and increased mortality following CABG surgery (Lamm et al 2007)<sup>59</sup>. The sponsor presented evidence purportedly ruling out the observations of Lamm et al (2007); however, these were not submitted in the original application and thus could not be used to inform on this issue. The sponsor stated that, based on such studies, improper fibrin sealant thawing and potential misuse of the fibrin sealant cannot be completely ruled out. The sponsor suggested that labelling changes will be implemented to ensure the correct preparation technique and enforce the existing warning against intravascular application of the fibrin sealant.

The sponsor stated that the use of fibrin sealant is a predictor and not the cause of increased mortality and that the application of a fibrin sealant in coronary surgery needs to be always based on a thorough product and application knowledge and critical individual risk benefit assessment.

The evaluators remained concerned by the cardiovascular safety profile of Tisseel. Although no causal link has been definitely proven between the use of fibrin glue and increased mortality following CABG surgery such a link has not been disproven and thus caution should be taken when using Tisseel in this setting.

*Is the sponsor aware of any specific drug-drug interactions between Tisseel and any other substances?*

The sponsor stated that specific drug-drug interactions have never been reported. However, the sponsor did not state how these data would be collected and did not explicitly state that there are no known drug-drug interactions.

*The drug-device interaction between Tisseel and the spray applicator has been highlighted in the submission. Is the sponsor aware of any additional drug-device interactions?*

With regards to drug-device interactions, the sponsor claimed that no report regarding the interaction between application device and Tisseel has become evident. The sponsor further stated that there is no evidence regarding interaction with devices or drugs used before, during or after surgical procedures.

The evaluators were unsure as to which preclinical studies the sponsor refers. The evaluators reiterated the sponsors acknowledgment that there exists a potential drug-device interaction when applying Tisseel using a spray device, and that a statement to this effect has been included in the Australian PI.

*The PSUR data indicated that several cases of infection (HIV and hepatitis B and C) occurred in patients who had received Tisseel. Due to the amalgamated nature of the data, the evaluators could not confirm whether these events occurred in patients who received Tisseel VH/SD or in patients who received other Tisseel formulations. Could the sponsor clearly detail the infections that occurred in patients who received Tisseel VH/SD?*

The sponsor did not refute the statement that cases of HIV and hepatitis B and C occurred in patients who had received Tisseel (whether related or unrelated to use of the product).

The evaluators noted that the formulations in which those cases of infection did occur were not specified; however no reports of Hepatitis A, B or C, HIV or Parvo B19 have been received when using the new formulation (Tisseel VH/SD)

*Case series data indicated that cord/canal oedema occurred commonly (42%). Does the sponsor have any evidence, published or otherwise, to inform on this issue?*

The sponsor stated that the 42% occurrence of cord/canal oedema reflects a common local reaction to surgery rather than to Tisseel. The sponsor also noted that this rate was lower compared to the incidence of these changes seen in asymptomatic patients not treated with Tisseel. The evaluators noted that expert clinical input confirms that cord/canal oedema does indeed represent a common local reaction to surgery.

*The safety of Tisseel when used in children, females (particularly those who are pregnant or breastfeeding), those deemed unsuitable to receive the surgical technique of interest, those with contraindications to surgery or general anaesthesia, and the elderly remains unclear. Does the sponsor have any evidence, published or otherwise, to inform on the safety of Tisseel in these populations?*

The sponsor did not consider it necessary to provide a separate clinical development program for paediatric populations. Several reasons were provided to support this argument:

- Tisseel is a topical haemostat for which dosing is dependent on the surface of the lesion.
- fibrin sealants have been used extensively in children in a variety of surgical specialties.
- pharmacovigilance data from Baxter's fibrin sealants do not indicate increased safety risk or lack of efficacy in children.
- Tisseel acts independent of the coagulation status of patients.

The sponsor provided further evidence in the form of published and internal studies; however, these data were not submitted with the original application and thus could not be used to inform on this issue. A table reporting the incidence of ADRs and serious ADRs in global postmarketing surveillance data in children between November 1991 and February 2011 was presented. However, this included the total number of paediatric and adult patients who experienced ADRs and was not expressed as a percentage of the total number of patients who had received Tisseel. Hence, a comparison of incidence between these populations was not possible.

The sponsor stated that the safety of fibrin sealants for use in human pregnancy or lactation has not been established in controlled clinical trials. The sponsor provided four publications which present evidence on the safety of Tisseel in this population; however, these studies were not provided in the original application and thus could not be used to inform on this issue. The sponsor stated that Tisseel should be administered to pregnant and lactating women only if clearly needed.

The sponsor considered Tisseel to be suitable for use in geriatric populations for the following reasons:

- it has been demonstrated in clinical studies in this patient population.
- it is a topical haemostat for which dosing is dependent on the surface of the lesion.
- it acts independent of the coagulation status of patients.

The sponsor provides reference to an internal study to provide evidence in support of this claim; however, this study was not provided in the original application and thus could not be used to inform on this issue.

Regarding patients who are contraindicated for surgery, the sponsor stated that the use of Tisseel does not imply the need for surgery when applied topically, as long as the wound/tissue can be accessed non surgically. The sponsor claimed that as Tisseel is not a systemic acting drug there should be no difference in safety profile in general patients and those contraindicated for surgery. However, no data were provided to support this statement.

The evaluators maintained that the use of Tisseel VH/SD has not explicitly been proven to be safe in paediatric, pregnant/lactating and geriatric populations. As a result, the suggestion that the product has an unproven safety profile in female, paediatric and geriatric populations will remain in place.

*Does the sponsor plan to provide a paediatric development program? If not, why not?*

No, the sponsor does not plan to provide a paediatric development program. The sponsor considered it unnecessary for the reasons presented in response to the previous question.

The evaluators recommended that the sponsor develop a paediatric development program in order to demonstrate the safety of Tisseel VH/SD in this population.

*The evaluators note that a wide variety of coatings are available, including titanium, beta glucan, omega-3 and collagen. Could the sponsor provide any evidence, published or otherwise, to inform on any drug-drug interactions between Tisseel and various mesh coatings?*

The sponsor stated that Tisseel has been used for fixation of various coated meshes and no drug-drug interaction has been reported. The sponsor referred to the answer provided above; however, this discusses efficacy rather than drug-drug interactions.

*The evaluators note that there is a possible learning curve associated with the uptake of Tisseel and this may impact upon its safety profile. Does the sponsor plan to provide any practical education to clinicians in the use of Tisseel?*

The sponsor outlined a plan to provide practical education to clinicians regarding the use of Tisseel for hernia operations. These consist of peer-to-peer programs whereby surgeons with experience using Tisseel will be required to provide didactic presentations to other surgeons on the use of Tisseel; training for Registrar surgeons (50% didactic lectures and 50% live laboratories); education of nurses both in and outside of a hospital setting (including how to thaw and prepare the product and delivery systems); and through a product website.

The evaluators noted that no timelines were presented and it was not specified which hospitals or clinics would receive such education (for example, all centres using or anticipated to use Tisseel VH/SD or only high volume centres).

### **PI and CMI**

There were also questions posed relating the proposed PI and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

## **Clinical Summary and Conclusions**

### **Assessment of benefits**

The benefits of Tisseel in the proposed usage are:

- a reduction in chronic pain. This was demonstrated in patients undergoing non iatrogenic abdominal wall hernia repair when Tisseel was used for mesh fixation compared with standard mesh fixation methods
- improvements in secondary outcomes including a quicker return to work or usual activities; a higher level of patient satisfaction with the surgery; a reduction in groin discomfort; a reduction in numbness; and a reduction in early and mid term postoperative pain. These were demonstrated in patients undergoing non iatrogenic abdominal wall hernia repair when Tisseel was used for mesh fixation, compared with standard mesh fixation methods.

### **Assessment of risks**

The risks of Tisseel in the proposed usage are:

- potential for immune response, including anaphylaxis.

- potential stronger, secondary immune response when applied more than once.
- potential for virus transmission.
- thromboembolic risk associated with intravascular application.
- potential for gas/air embolism when applied by spraying.
- possible learning curve associated with the uptake of Tisseel.
- possible product inefficacy (as reported in PSUR data).
- potential off-label use.
- unproven safety in female, paediatric and elderly patients.
- unknown potential interactions between mesh coatings other than C-Qur or Dualmesh (such as beta glucan) and Tisseel.
- unknown efficacy when used in conjunction with non stick meshes.

### **Assessment of benefit risk balance**

The benefit risk balance of Tisseel is unfavourable given the proposed usage but would become favourable if the changes recommended below are adopted.

Regarding primary efficacy outcomes, the use of Tisseel for mesh fixation during inguinal hernia repair demonstrates a favourable effect on chronic pain compared with standard mesh fixation methods.

Regarding secondary efficacy outcomes, the use of Tisseel for mesh fixation during inguinal hernia repair demonstrated a favourable effect on time to return to work or usual activities; patient satisfaction with the surgery; groin discomfort; numbness; and early and mid term postoperative pain after inguinal hernia repair using Tisseel for mesh fixation, when compared with standard mesh fixation methods.

Additionally, the evaluators noted that the efficacy of Tisseel when used in conjunction with non stick meshes is unknown.

The PSUR data reported that several instances of Tisseel inefficacy occurred. It may be prudent to advise surgeons that an alternative mesh fixation method (sutures, staples or tacks) should be available during the operative procedure, in case of Tisseel inefficacy.

Several treatment related and SAEs were reported in the current submission. Although the remaining events seen in Tisseel patients were generally mild, the evaluators noted that the Risk Management Plan (RMP) and the PSUR data both indicate that events such as HIV/hepatitis B/hepatitis C infection, anaphylaxis and air embolism have occurred after the use of Tisseel. Due to the aggregated nature of these data, it is unclear which formulation of Tisseel was associated with these viral transmissions. The evaluators noted that the proposed PI instructs clinicians to record the batch number of Tisseel used in case of infection. The sponsor did not provide any data to inform on any potential immune response relating to repeated application of Tisseel.

The evaluators noted the potential that Tisseel may be used for indications beyond those approved by the TGA. Both the PSUR and MAUDE data revealed that Tisseel has been used in an off label manner in at least 30 instances. However, as these data are reported voluntarily and the population is of uncertain size, the frequency of off-label use may be much higher.

Generally, the studies did not provide details regarding particular properties of the mesh used during hernia repair. As such, it is presently unclear whether there are potential interactions between Tisseel and the various mesh coatings used.

### Recommendation regarding authorisation

The evaluators recommended approval subject to changes or conditions. Firstly, the evaluators recommended a narrowing of the broad proposed indication to reflect the indication in which efficacy was satisfactorily demonstrated (mesh fixation in inguinal hernia repair). The evaluators considered that the efficacy of Tisseel for mesh fixation in inguinal hernia repair is likely to apply to other non iatrogenic abdominal wall hernias, including femoral and umbilical hernias. However, the effectiveness of Tisseel for mesh fixation has not been satisfactorily demonstrated in incisional hernias. Additionally, the proposed indication does not include tacks as an alternative mesh attachment method, which the evaluators consider to be inconsistent with current Australian practice. Therefore, the evaluators recommend that the indication for Tisseel should be amended to:

*mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative or adjunct to sutures, staples or tacks.*

## V. Pharmacovigilance Findings

### Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

### Safety Specification

The summary of the ongoing safety concerns as specified by the sponsor is shown in Table 12.

**Table 12: Summary of ongoing safety concerns**

<b>Important Identified Risks:</b>	Allergic Reactions Thromboembolic events due to inadvertent intravascular application
<b>Important Potential Risks:</b>	Medication Errors Risk of transmission of infective agents Granulation tissue formation due to application of excess product Suboptimal application technique during hernia repair Risk of air embolism, tissue rupture, and gas entrapment with compression with the use of spray devices
<b>Important Missing Information:</b>	Interaction with other medicinal products; incompatibilities Preclinical studies regarding subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation.



After receiving comment from the clinical and nonclinical evaluators, the OPR reviewer noted that the summary of the ongoing safety concerns was considered acceptable.

### **Pharmacovigilance Plan**

Routine pharmacovigilance is proposed to monitor all safety concerns.<sup>76</sup> This was considered acceptable.

### **Risk minimisation activities**

In the RMP, the sponsor does not make any conclusions about the need for risk minimisation activities. However, a conclusion has been submitted with responses to questions along with an assurance that this conclusion will be included in the next update of the RMP. The sponsor concludes that additional risk minimisation activities are required to ensure the appropriate use and application technique of Tisseel during hernia repair. The remaining risks will have routine risk minimisation activities.<sup>77</sup>

The sponsor's conclusions were considered acceptable.

Additional risk minimisation activities were proposed for appropriate use and application technique of Tisseel during hernia repair, specifically for the safety concerns:

- Suboptimal application technique
- Thromboembolic events due to inadvertent intravascular application
- Granulation tissue formation due to application of excess product
- Risk of air embolism, tissue rupture, and gas entrapment with compression with the use of spray devices

These activities involve instructions for use, training videos, information on the Tisseel Hernia Website<sup>78</sup> and including safety information during educational presentations.

The educational program was developed by a consultant surgeon who specialises in hernia and hepatobiliary surgery.

The OPR reviewer recommended that the sponsor considers the use of these additional risk minimisation activities for all indications and not solely for hernia repair.

### **Conclusion**

The sponsor proposes to monitor the effectiveness of the educational program via routine monitoring of postmarketing AEs for a two year period. It was recommended to the Delegate that the sponsor include a sub analysis of the safety concerns relating to appropriate use and application technique in the PSURs for the first 3 years following registration.

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<sup>76</sup> Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

<sup>77</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

<sup>78</sup> The sponsor commented that this website is only for the United Kingdom market and there are no immediate plans to do an Australia-New Zealand website

## VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

There was no requirement for a quality evaluation in a submission of this type.

### Nonclinical

The submission included published data on the use of Tisseel in nonclinical models of hernia repair. The data indicated that Tisseel is unlikely to be effective when used alone in hernia repair techniques that involve the adhesion of mesh to an intact peritoneum. The Delegate proposed to address this issue through a precautionary statement in the PI. Otherwise there were no objections to approval of the new indication.

### Clinical

#### Clinical evaluation

The clinical evaluators recommended approval of the application, with an amended indication. The clinical data submitted in support of the application were mostly obtained from the published literature. There was also one unpublished study for which a company study report was provided.

#### Efficacy

From the clinical data submitted by the sponsor, the evaluators identified five trials which they considered to be pivotal efficacy studies. In the opinion of the evaluators, the most clinically important outcome measures in studies of hernia repair are hernia recurrence and chronic pain. The studies have therefore been assessed against these criteria.

#### *Campanelli 2009*

This was the one submitted trial for which there was a company clinical study report. It was a prospective, randomised, double blind, parallel group design, controlled trial conducted in 325 male subjects undergoing inguinal hernia repair. Patients were randomised to have mesh fixation either by sutures or by application of Tisseel. The Tisseel was applied by spraying. The trial was designed as a superiority trial with the aim of establishing superiority of Tisseel over sutures.

At 12 months post surgery there was no difference between groups in:

- mean VAS pain scores or the incidence of patients with no pain;
- the incidence of hernia recurrence (1 in the Tisseel group and 2 in the sutures group).

There was a suggestion of improved outcomes in the Tisseel group according to some secondary endpoints:

- reduced incidence and severity of numbness at 12 months;
- reduced severity of 'groin discomfort' at 12 months;
- increased level of patient satisfaction (98.1% versus 91.6% ).

Overall the study failed to demonstrate superiority of Tisseel over sutures but suggested that the two methods have comparable outcomes.

**Hidalgo 2005**

This was a prospective study which enrolled 55 subjects with bilateral inguinal hernias. Each patient served as his own control, with Tisseel being used for mesh fixation on the left side and sutures on the right. Tisseel was applied through a catheter or by the spraying method.

At 12 months there were no hernia recurrences and no patient had chronic pain.

**Lau 2005**

This was a prospective study which randomised 93 patients with bilateral inguinal hernias to mesh fixation with either staples (n=47) or Tisseel (n=46). The surgical technique used was endoscopic hernia repair and the Tisseel was applied using a laparoscopic catheter.

- at a median follow-up of 1.2 years there were no hernia recurrences in either group;
- there was no difference in the incidence of chronic pain (Tisseel 13.2% versus staples 20.0%) after a median follow up of 2 years.

**Lovisetto 2007**

This was a prospective study in which 197 subjects with inguinal or femoral hernia were randomised to mesh fixation by either staples (n=98) or Tisseel (n=99). The surgical technique used was endoscopic hernia repair and the Tisseel was applied using a laparoscopic catheter.

- there was one hernia recurrence in the Tisseel group and none in the Staple group;
- VAS pain scores were significantly lower in the Tisseel group at 3 and 6 months.

**Olmi 2007**

This was a prospective study in which 600 subjects with inguinal hernia were randomised to mesh fixation by Tisseel (n=150) or one of three staple methods (n=150 each group). The surgical technique used was endoscopic hernia repair and the Tisseel was applied using a laparoscopic catheter.

At one month post surgery there were three hernia recurrences in one of the Staple groups, and none in the other three groups. Chronic pain was not an outcome measured in this study.

The application included several other studies which could not be considered as pivotal due to their design (for example, the use of non randomised controls) or inadequate reporting. Although some of these studies reported more favourable outcomes with Tisseel than the comparator, the findings cannot be considered reliable due to flaws in study design and reporting.

**Safety**

A total of 22 studies provided safety data. In these studies, a total of 2586 subjects were treated with Tisseel.

Adverse events occurring in the five pivotal studies are summarised in Table 8. Adverse events occurring in the other studies submitted are summarised in Tables 9 and 10.

Overall, the adverse event data did not raise any new safety concerns specifically related to the use of the product in hernia surgery. Some of the five pivotal studies suggested that the use of Tisseel may be associated with less post operative pain than sutures or staples.

## Risk Management Plan

The Risk Management Plan submitted with the application has been found to be acceptable by the TGA's Office of Product Review.

## Risk-Benefit Analysis

### Delegate Considerations

#### *Assessment of benefits and risks*

The five pivotal studies established that the efficacy of Tisseel is comparable to that of sutures or staples for fixation of mesh in hernia repair, in terms of hernia recurrence or incidence of chronic pain. In one of the pivotal studies (Lovisetto 2007), Tisseel was associated with a reduced incidence of chronic pain compared to staples.<sup>49</sup> Some of the pivotal studies also suggested that use of Tisseel may be associated with a reduced incidence of acute postoperative pain. The submitted studies did not identify any particular safety concerns associated with use of Tisseel for the new indication. The Delegate therefore considered that the benefit risk ratio for the new indication is favourable and proposed to approve the application.

#### *Indication*

The Delegate proposed to approve the indication recommended by the clinical evaluators:

*For mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks.*

#### *Administration by spraying*

In two of the pivotal studies (Campanelli 2009 and Hidalgo 2005), Tisseel was administered by spraying.<sup>44,47</sup> As evidence of efficacy and safety of this method of administration has now been provided, the Delegate proposed to approve its use.

### Response from sponsor

The sponsor accepted the Delegate's recommendation to revise the wording of the indication as follows (changes are in bold font):

*Tisseel is indicated:*

- *as adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical; and*
- *as a sealant as an adjunct for closure of colostomies.*
- *as a sealant and/or adhesive for use in autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) procedures.*
- *For mesh fixation in **non-iatrogenic** abdominal wall hernia repair, as an alternative to sutures, **or staples or tacks.***

The sponsor also accepted all the Delegate's recommendations to revise the Product Information (PI) and Consumer Medicine Information (CMI) documents.

### Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

**Efficacy and Safety**

The ACPM agreed with the Delegate that clinical efficacy has been demonstrated for this product.

**Indication**

The ACPM considered this product to have a positive benefit risk profile for the indication of:

*For mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks.*

The ACPM advised that the implementation by the sponsor of the recommendations to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Tisseel VH/SD would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Tisseel VH S/D containing fibrin sealant for the new indication:

*For mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks.*

The full indications are now as follows:

- *as adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical;*
- *as a sealant as an adjunct for closure of colostomies;*
- *as a sealant and/or adhesive for use in autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) procedures;*
- *for mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks.*

**Specific Conditions Applying to these Therapeutic Goods:**

1. It is a condition of registration that the sponsor implements in Australia the fibrin sealant VH S/D Risk Management Plan (RMP), dated 12 January 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
2. It is a condition of registration that the sponsor monitors the effectiveness of the proposed educational program for the appropriate use and application technique of Tisseel VH/SD, by including a sub-analysis for the related safety concerns in the PSURs for the first 3 years following this approval.

**Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605  
[www.tga.gov.au](http://www.tga.gov.au)

Reference/Publication #

# TISSEEL

## NAME OF THE MEDICINE

### TISSEEL [Fibrin Sealant]

Two-Component Fibrin Sealant, Deep-Frozen, Vapour Heated (VH) and Solvent Detergent (S/D) treated, TISSEEL VH S/D<sup>1</sup>

## DESCRIPTION

The active ingredients of TISSEEL VH S/D are formulated as two sterile, deep-frozen solutions, the Sealer Protein Solution and Thrombin Solution (see Table 1 below for composition of TISSEEL). Each solution is presented in a separate preloaded chamber of one double-chamber syringe. The active ingredients are fractionated from pooled human plasma.

**Table 1: Composition of TISSEEL**

	Sealer Protein solution	Thrombin Solution
Active Ingredients	-Aprotinin (synthetic) -Factor XIII -Fibrinogen	-Thrombin (human) -Calcium chloride (2 H <sub>2</sub> O)
Excipients	-Albumin (human) -Histidine -Nicotinamide -Polysorbate 80 -Sodium citrate -Water for injections	-Albumin (human) -Sodium chloride -Water for injections

The two deep frozen solutions comprising TISSEEL must be defrosted prior to use. After thawing and warming up to 37 °C, the two solutions are mixed during application (see DOSAGE AND ADMINISTRATION section, heading Method of Application).

## Chemical structures

The major component of the clottable protein (human origin) is fibrinogen. The fibrinogen molecule is a dimer composed of two symmetrical subunits linked by -S-S- bonds. It could be written in a simple formula as (A $\alpha$ , B $\beta$ ,  $\gamma$ )<sub>2</sub> and has a molecular weight (MW) of about 340 000. The A $\alpha$ -chain contains 610 amino acids (MW about 68 000), the B $\beta$ -chain 461 amino acids (MW about 57 000), and the  $\gamma$ -chain 411

<sup>1</sup> The term 'Vapour Heated (VH) and Solvent Detergent (S/D) treated' is abbreviated as VH S/D

amino acids (MW about 47 000). Thus, the entire human fibrinogen contains 2964 amino acids.

Thrombin (human origin) is a glycosylated protein, consisting of two polypeptide subunits A and B, covalently linked by one -S-S- bond. The molecular weight is about 33 800. The human thrombin subunit A chain is made of 36 amino acids, whilst the B chain contains 259 amino acids.

Factor XIII (human origin), also called blood-coagulation factor XIII, is a tetramer composed of two a-chains and two b-chains (each of a molecular weight of about 80 000) which are non-covalently associated.

Aprotinin (synthetic origin) is a protease inhibitor, a polypeptide consisting of one chain of 58 amino acids with a molecular weight of 6511.5, also stabilized by -S-S- bonds.

## PHARMACOLOGY

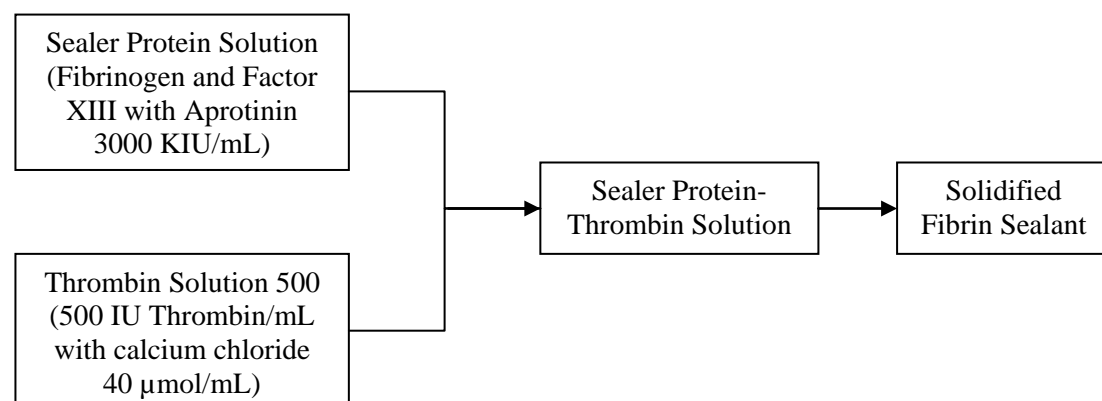
### Pharmacodynamics

TISSEEL contains two components, Sealer Protein Solution and Thrombin Solution. The Sealer Protein Solution contains fibrinogen as the main active ingredient, the active ingredient of the Thrombin Solution is human Thrombin.

Thrombin is a highly specific protease that transforms the fibrinogen contained into fibrin monomers. These fibrin monomers are then polymerized in a linear fashion and stabilised by cross-linking (catalysed by factor XIII) to form an insoluble fibrin clot. Aprotinin (synthetic) is a protease inhibitor which prevents the premature degradation of fibrin.

These reactions simulate the key features of the physiological coagulation process. The resulting fibrin clot appears as a white, elastic mass which firmly adheres to tissue and which can be used to achieve haemostasis or seal tissues.

When the two component solutions come into contact, conversion of fibrinogen to fibrin, and polymerization and cross-linking of fibrin monomers commences immediately and results in the clotting of the fibrin within seconds. The following diagram illustrates the process.





## Pharmacokinetics

Solidified TISSEEL VH S/D is intended for local application only, therefore systemic exposure or distribution to other organs or tissues is not expected and pharmacokinetic studies were not conducted.

## CLINICAL TRIALS

TISSEEL VH S/D was evaluated in a prospective, parallel design, randomised (1:1), double-blind, multicenter clinical study against an earlier formulation of the product, TISSEEL VH<sup>2</sup>, in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) and median sternotomy. Patients were treated with TISSEEL VH S/D or the control product TISSEEL VH only when haemostasis was not achieved by conventional surgical methods. For the end point, haemostasis achieved at the primary treatment site within 5 minutes of treatment and maintained until closure of the surgical wound, TISSEEL VH S/D was non-inferior to the earlier formulation of the product using a one-sided 97.5% confidence interval on the difference in the proportion of subjects successfully treated.

Haemostasis within 5 minutes and maintained until surgical closure		
	TISSEEL VH S/D	TISSEEL VH
Intent to Treat Analysis	127/144 (88.2%)	129/144 (89.6%)
Per Protocol Analysis	108/123 (87.8%)	122/135 (90.4 %)

## Virus Safety

To confirm virus safety of TISSEEL VH S/D, subjects were followed up for seroconversion due to virus infections. There were zero confirmed seroconversions for both TISSEEL VH S/D-treated subjects and TISSEEL VH-treated subjects: analysis of B19V seroconversion 1 month after surgery revealed a 0% (0/140) incidence of seroconversion in TISSEEL VH S/D-treated subjects and a 0% (0/138) incidence of seroconversion in TISSEEL VH-treated subjects. Analysis of HAV, HBV, HCV, and HIV-1/-2 six months after surgery revealed a 0% (0/128) incidence of seroconversion in TISSEEL VH S/D-treated subjects and a 0% (0/134) incidence of seroconversion in TISSEEL VH-treated subjects.

An earlier formulation of TISSEEL VH S/D, TISSEEL HT (Fibrin Sealant heat-treated) was evaluated in an open-label crossover study against control topical haemostatic agents in 489 patients undergoing cardiovascular re-operation or re-sternotomy at 11 institutions. Patients were randomised to TISSEEL HT or control haemostatic agents when a topical haemostatic was needed at the conclusion of

<sup>2</sup> Baxter commercialized several single virus inactivated, predecessor fibrin sealant products, utilizing heat treatment (HT) or vapor heat treatment (VH) for virus inactivation. Predecessor products were manufactured both in frozen or lyophilized presentation.

surgery and after all attempts of surgical haemostasis. Patients were crossed to the alternative therapy if bleeding continued after the 5 minute endpoint. At 10 centres, TISSEEL was used after administration of protamine sulfate. At one site, TISSEEL could be used before administration of protamine sulfate. 365 of the 489 patients had an eligible bleeding event, for the primary endpoint, successful haemostasis at 5 minutes, TISSEEL was statistically significantly superior to control topical haemostatic agents:

Haemostasis within 5 minutes	
TISSEEL HT	Control Topical Hemostatic Agent
159/193 (82.4%)	76/172 (44.2%)
Pearson $\chi^2$ , two sided; $p < 0.0001$ ; intent-to-treat analysis	

Similarly, absolute time to cessation of bleeding was statistically significantly shorter for TISSEEL than for control topical haemostatic agents ( $p < 0.0001$ , Wilcoxon-Gehan test, two sided).

In a single centre, open label trial, an earlier formulation of TISSEEL was compared to historical controls in patients undergoing laparotomy for blunt or penetrating traumatic injury to the spleen and/or liver. Use of TISSEEL resulted in the need for statistically significantly fewer splenectomies than control haemostatic manoeuvres:

Splenectomy Rate		
Injury to:	TISSEEL	Historic Controls
Spleen $p < 0.001$	0/19	14/22
Spleen and liver $p < 0.001$	1/26	19/34

TISSEEL did not result in statistically significantly reduced mortality in patients with blunt or penetrating trauma to the liver alone or to the liver and spleen ( $p = 0.067$ ,  $\chi^2$ , one sided).

In a single centre, prospective open label study of 120 patients randomised to standard of care (59 patients) or standard of care plus Fibrin Sealant (61 patients) for elective colostomy closure after temporary colostomy placement for treatment of traumatic injury to the colon, the earlier version of TISSEEL plus standard of care was shown to be statistically significantly superior to standard of care alone ( $p = 0.0406$ , Jonckheere-Terpstra test for ordinal data, two sided) with regard to anastomotic complications (leakage, intra-abdominal abscess formation, re-operation, septic shock, and death).

A review of published literature was conducted studying the repair of defects of the articular cartilage in the knee; (n= 293 patients; 166 patients were treated with either Autologous Chondrocyte Implantation (ACI) or Matrix-Induced Autologous

Chondrocyte Implantation (MACI); 127 patients were treated with either mosaicplasty or microfracture or abrasive arthroplasty). In all ACI/MACI procedures, TISSEEL Fibrin Sealant was applied topically. The efficacy of TISSEEL has been assessed indirectly by the efficacy outcome measures used to assess joint function following repair of cartilage defects. Outcome measures within the first six months of treatment are considered to be of particular importance because treatment failure attributed to graft movement (e.g., periosteal delamination or detachment of the collagen matrix) typically occurs within the first three to six months following implant. In addition, in the first 6 months post-implant, there were no reports by patients of symptoms which may be indicative of graft instability such as “locking” or “catching” of the knee joint. In one study MRI assessments, made at one and two months, showed that there was a high level of graft integration with the surrounding cartilage, and that grafts were present and in their original position in the majority of patients (15/17). These findings suggest that TISSEEL is an effective adhesive in this indication. Long term results ( $\geq 6$  months) indicated that treatment with either ACI or MACI was at least as successful as the comparative treatment.

### Hernia repair

A prospective, multi-centre, randomized, double-blinded, parallel, controlled clinical trial (Campanelli 2009) involving 325 male subjects was conducted to evaluate the safety and effectiveness of TISSEEL in uncomplicated unilateral or bilateral, direct or indirect primary inguinal hernia using the Lichtenstein technique. Patients were randomized to have mesh fixation either by sutures or by application of TISSEEL. For the clinically important outcomes of chronic pain and recurrence as well as for pain / no pain the results of the statistical analyses are as follows:

Chronic pain (VAS, in mm (STD))	ITT		p	PP		p
	TISSEEL	Sutures		TISSEEL	Sutures	
6 months	6.35 (14.71)	10.56 (18.12)	0.0052	6.34 (14.79)	10.56 (18.12)	0.0040
12 months	3.87 (11.53)	5.93 (14.75)	0.1134	3.92 (11.60)	5.93 (14.75)	0.1259

No pain (VAS = 0)	ITT		p	PP		p
	TISSEEL	Sutures		TISSEEL	Sutures	
6 months	73.5% (108/147)	59.7% (92/154)	0.0049	73.8% (107/145)	59.7% (92/154)	n.a.
12 months	83.9% (125/149)	76.7% (115/150)	0.1104	83.7% (123/147)	76.7% (115/150)	n.a.

Recurrence	ITT	
	TISSEEL	Sutures
	1/159	2/160

A prospective, single-centre, comparative clinical trial by Hidalgo et al (2005) of 55 subjects aimed to assess the feasibility of TISSEEL for mesh fixation in hernia repair using the Lichtenstein technique. Only subjects who had bilateral inguinal hernias were eligible: Sutures were used on the right side and TISSEEL on the left side. The

primary efficacy outcomes investigated – recurrence rates at month 12 and chronic pain – did not occur during the study period in either group.

Lau (2005) conducted a single-centre, randomized (1:1), controlled clinical trial to compare the clinical outcomes of simultaneous bilateral endoscopic totally extraperitoneal (TEP) inguinal hernia repair using either an earlier version of TISSEEL or staples for mesh fixation in 93 subjects. Efficacy outcomes were recurrence rate and chronic groin pain. At a median follow-up of 1.2 years there were no incidences of hernia recurrence in either treatment group. The difference in incidence of chronic pain for the 78 subjects assessed at median 2 year follow-up was not significant (TISSEEL 5/38, 13.2% (95% CI 2.5% - 23.9%), and staples 8/40, 20% (95% CI 7.6% - 32.3%)) (p=0.418).

In a prospective single-centre controlled clinical trial by Lovisetto et al (2007), 197 subjects with uni- or bilateral inguinal or femoral hernia underwent laparoscopic transabdominal preperitoneal (TAPP) hernioplasty and were randomized to mesh fixation by either staples (n=98) or TISSEEL (n=99). TISSEEL was applied via a laparoscopic catheter.

The primary efficacy outcomes were early postoperative and late neuralgia recorded using a visual analogue scale (VAS): At 1, 3, and 6 months after surgery, the mean VAS score was significantly lower in the TISSEEL group compared with the staples group:

Neuralgia (mean VAS score [mm])	TISSEEL	staples	p
1 month	19	26	< 0.05
3 months	11	23	< 0.001
6 months	11	20	< 0.001
12 months	(8)	(12)	n.a.

Secondary outcomes included:

	TISSEEL	staples	p
Recurrence	1	0	n.a.

A single-centre, prospective, randomized (1:1:1:1), controlled study by Olmi et al (2007) compared pain outcomes in 600 subjects who were treated with Protak (Tyco, Norwalk, CT; group A, n=150 (189 hernias)), EndoANCHOR (Ethicon Endo-Surgery, Inc., Cincinnati, OH; group B, n= 150 (198 hernias)), Endopath Multifeed Stapler (EMS) 10 mm shaft (Ethicon Endo-Surgery, Inc., Cincinnati, OH; group C, n=150 (222 hernias)), or TISSEEL (Baxter Healthcare Corporation, Deerfield, IL; group D, n=150 (222 hernias)) for mesh fixation during laparoscopic TAPP uni- or bilateral inguinal hernia repair. Subjects were followed up to 1 month after surgery for recurrence, postoperative pain on a 10-point VAS, operating time, length of stay, and return to work.

A total of 3 recurrences occurred in the study, all of which occurred in group C (n.s.).

The postoperative (24 – 72 hours) pain score in group D (VAS 2) was markedly lower than in groups A (VAS 5-7), B (VAS 4-5), and C (VAS 3-4).

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## INDICATIONS

TISSEEL is indicated:

- as adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical; and
- as a sealant as an adjunct for closure of colostomies
- as a sealant and/or adhesive for use in autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) procedures
- For mesh fixation in non-iatrogenic abdominal wall hernia repair, as an alternative to sutures, staples or tacks

## CONTRAINDICATIONS

Known hypersensitivity to aprotinin or known hypersensitivity to any other component of TISSEEL.

Injection of TISSEEL into tissues is contraindicated. Such use has been associated with inadvertent intravascular injection, with thromboembolic complications. TISSEEL should be applied with caution to minimise any risk of intravascular application, for example in coronary bypass surgery. TISSEEL should only be applied topically.

Additionally, soft tissue injection of TISSEEL carries the risk of an anaphylactic reaction and/or local tissue damage.

## PRECAUTIONS

### Viral and Prion Risk

Sealer Protein Concentrate and Thrombin are made from human plasma. Products made from human plasma may contain infectious agents which can cause disease, such as viruses and theoretically, the agent that causes Creutzfeldt-Jakob Disease (CJD) in humans. 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.

The measures taken (including double virus inactivation by vapour heat treatment and solvent detergent treatment) 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 small non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red blood cell turnover (e.g., hemolytic anaemia).

It is strongly recommended that every time a patient receives a dose of TISSEEL, the name and batch number of the product are recorded in order to maintain a record of the batches used.

All infections thought by a clinician possibly to have been transmitted by TISSEEL should be reported by the clinician or other healthcare provider to Baxter.

Patients should be instructed to consult their clinician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose, followed about two weeks later by a rash and joint pain).

## General

Administration of TISSEEL may result in allergic reactions in some patients. For patients with a known allergic diathesis, a history of hypersensitivity to medical products or a history of having previously received aprotinin-containing products (including previous use of TISSEEL) a careful risk-benefit assessment should be carried out prior to administration. The risk of immunisation against proteins such as aprotinin is increased if repeated exposure occurs within six months. If it is decided to proceed with treatment in such patients, prior administration of antihistamines should be considered.

Manifestations of hypersensitivity reactions to TISSEEL observed include: bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnea, nausea, urticaria, angioedema, pruritus, erythema, paresthesia. Fatal anaphylactic reactions, including anaphylactic shock, have also been reported with TISSEEL. Refer ADVERSE EFFECTS. Intravascular application might increase the likelihood and severity of acute hypersensitivity reactions in susceptible patients. Because of the risk of intravascular injection, the product must not be injected into highly vascularised tissue, such as nasal mucosa.

The new formulation of TISSEEL contains synthetic aprotinin. As synthetic aprotinin is structurally identical to bovine aprotinin, the use of TISSEEL in patients with allergies to bovine proteins should be carefully evaluated.

Air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening, have occurred with the use of spray devices employing a pressure regulator to administer TISSEEL. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

When applying TISSEEL using a spray device, be sure to use the pressure within the pressure range recommend by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 1.4-1.7 bars (20—25 psi). Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying TISSEEL, changes in blood pressure, pulse,

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oxygen saturation and end tidal CO<sub>2</sub> should be monitored because of the possibility of occurrence of air or gas embolism.

As Sealer Protein and Thrombin Solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals (e.g. in disinfectants), any such substances should be removed before application. Refer INCOMPATIBILITIES.

TISSEEL alone is not indicated for the treatment of severe or brisk arterial or venous bleeding. When used in these situations, TISSEEL is likely to be washed away in the flow of blood before haemostasis can be attained.

If possible, cover all tissue adjacent to the site of sealing before applying TISSEEL.

TISSEEL should not be used for the sealing of neuroanastomoses, as the high aprotinin content of the TISSEEL solution delays absorption of the fibrin seal and it cannot be ruled out that this may cause fibrosis.

Injection into the nasal mucosa must be avoided, as severe allergic/anaphylactoid reactions have been observed and thromboembolic complications may occur in the area of the ophthalmic artery.

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

The safety and effectiveness of TISSEEL used alone or in combination with biocompatible carriers in neurosurgical procedures or other surgeries involving confined spaces have not been established. There have been rare reports of serious adverse events such as paralysis and other compressive complications possibly related to the use of fibrin sealants in combination with resorbable haemostatic agents.

If fibrin sealants are applied in confined bodily spaces, the risk of compressive complications should be taken into account.

### **Use in hernia**

Nonclinical data indicate that TISSEEL is unlikely to be effective when used alone for mesh fixation to peritoneum (e.g. with an intraperitoneal approach for laparoscopic ventral hernia repair). In such situations TISSEEL should only be used as an adjunct to sutures or staples/tacks.

TISSEEL is not effective when used with Omega 3 fatty acid-containing and non-porous ePTFE meshes. TISSEEL should not be used with these meshes. Furthermore, the efficacy of TISSEEL has not been demonstrated in meshes with other coatings, including with beta glucan.

### **Effects on Fertility**

Studies of the effect of TISSEEL on fertility have not been performed.



**Use in Pregnancy (Category B2)**

Animal reproduction studies have not been conducted with TISSEEL. There are no adequate and well-controlled studies in pregnant women. TISSEEL should be used during pregnancy only if clearly needed and potential benefit justifies the potential risk to the fetus.

**Use in Lactation**

Studies on TISSEEL in lactating animals or women have not been conducted. TISSEEL should be used during lactation only when strictly indicated.

**Paediatric Use**

Safety and effectiveness of TISSEEL in paediatric patients have not been established. There has been a single report of disseminated intravascular coagulation occurring in a premature infant who received TISSEEL 3 mL during a laparotomy for peritoneal adhesions.

**Use in the Elderly**

Of the total number of subjects in a clinical study of TISSEEL, 71 out of 144 subjects were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Genotoxicity**

Studies of genotoxic potential of TISSEEL have not been performed. Negative results were obtained in bacterial reverse mutation assays (Ames tests) conducted with various components of TISSEEL (sealer protein solution containing bovine aprotinin; synthetic aprotinin; human thrombin solution).

**Carcinogenicity**

Animal studies to evaluate the carcinogenic potential of TISSEEL have not been performed.

**INTERACTIONS WITH OTHER MEDICINES**

There are no known interactions between TISSEEL and other drugs. Efficacy has been demonstrated in fully heparinised patients undergoing cardiopulmonary bypass.

Oxycellulose containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials.

Refer to INCOMPATIBILITIES for more detailed information on interactions with substances other than drugs.

## ADVERSE EFFECTS

Anaphylactic and anaphylactoid reactions may occur in patients who have previously received a fibrin-based sealant, in those with a known hypersensitivity to aprotinin and those who have previously received aprotinin systemically. Even if the second treatment with TISSEEL was well tolerated, a subsequent administration of TISSEEL or systemic administration of aprotinin may result in severe anaphylactic reactions.

Symptoms associated with allergic/anaphylactic reactions include flushing, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnoea, severe hypotension, and anaphylactic shock. In the event of hypersensitivity reactions, administration of TISSEEL should be discontinued, the topical clot removed, and appropriate treatment instituted.

In rare cases, these reactions may also occur in patients receiving aprotinin or TISSEEL for the very first time.

Injection of TISSEEL into tissues has been associated with inadvertent intravascular administration and thromboembolic complications. Such use is therefore not recommended (see CONTRAINDICATIONS section).

The adverse reactions presented in this section were reported from clinical trials investigating the safety and efficacy of TISSEEL. In these trials, TISSEEL was administered for adjunct hemostasis in cardiac, vascular, and total hip replacement surgeries; and for the sealing of lymphatic vessels in patients undergoing axillary lymph node dissection. In these studies, a total of 499 patients were administered TISSEEL. The frequencies are based on the number of cases considered possibly/probably related by investigators.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	Preferred MedDRA Term	Frequency	Number of Cases (Frequency Percentage)
<b>VASCULAR DISORDERS</b>	<b>Hypotension</b>	Uncommon	1 (0.2%)
<b>GASTROINTESTINAL DISORDERS</b>	<b>Nausea</b>	Uncommon	2 (0.4%)
<b>INVESTIGATIONS</b>	<b>Fibrin degradation products increased</b>	Common	7 (1.4%)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>Post-procedural pain</b>	Common	7 (1.4%)

Legend: ADR frequency is based upon the following scale: Very Common ( $\geq 1/100$  -  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  -  $< 1/100$ ), Rare ( $\geq 1/10,000$  -  $< 1/1,000$ ), Very Rare ( $< 1/10,000$ )

## Post-marketing Adverse Reactions

The undesirable effects reported in the listing hereafter are based on post-market experience for this type of product.

The undesirable effects listed below reflect the type of undesirable effects that have been reported with TISSEEL.

### Cardiac disorders

- Bradycardia, tachycardia

### Gastrointestinal disorders

- Nausea

### General disorders and administration site disorders

- Hypersensitivity reactions

### Immune system disorders

- Hypersensitivity (including anaphylactic reactions, anaphylactic shock, and the following manifestations: angioedema, paresthesia, bradycardia, tachycardia, flushing, bronchospasm, dyspnea, wheezing, urticaria, pruritus, and erythema). Anaphylactic reactions and anaphylactic shock have included fatal outcomes

### Injury, poisoning and procedural complications

- Anaphylactoid reactions

### Skin and subcutaneous tissue disorders

- Pruritus, impaired healing

### Vascular disorders

- Thromboembolism, including cerebral artery embolism and venous thrombotic cerebral infarction\*

\* as a result of intravascular application into the superior petrosal sinus.

Class Effects

Other adverse reactions associated with the fibrin sealant/hemostatic class include:

- air or gas embolism as a result of intravascular application using pressurized gas
- as manifestations of hypersensitivity such as application site irritation, chest discomfort, chills, headache, lethargy, restlessness, and vomiting

**DOSAGE AND ADMINISTRATION****Dosage**

TISSEEL should only be administered topically. **Do not inject. Tisseel must not be applied intravascularly.** The required dose depends upon the size of the surface to be covered. To avoid the formation of excess granulation tissue, and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of TISSEEL should be applied. Excessive thickness of the fibrin layer may interfere with the product's efficacy and the wound healing process.

The application can be repeated, if necessary. However, avoid re-application of TISSEEL to a pre-existing polymerized TISSEEL layer as TISSEEL will not adhere to a polymerised layer. If used for tissue adherence, it is recommended that the initial application cover the entire intended application area.

The approximate surface areas covered by each package size of TISSEEL are listed in the following table:

Maximum size of the area to be sealed using cannula	Maximum size of the area to be sealed using compressed gas	Required package size of TISSEEL
8 cm <sup>2</sup>	100 cm <sup>2</sup>	2 mL
16 cm <sup>2</sup>	200 cm <sup>2</sup>	4 mL
40 cm <sup>2</sup>	500 cm <sup>2</sup>	10 mL

When TISSEEL is used for mesh fixation it may be applied as drops and/or by a spray technique depending on the preference of the surgeon. Usually the drops of TISSEEL are applied where surgeons routinely position staples and the layer of fibrin sealant achieved with spraying allows the entire mesh to be fixed in place without shrinking and folding.

The quantity of TISSEEL required for mesh fixation depends on the mesh size selected and the recommended amount is the same for different application techniques. For example, 2 – 4mL of reconstituted TISSEEL applied as a thin layer is suitable to adequately fix a standard size mesh of approximately 10 x 15 cm.

When using the drop technique, surgeons should apply TISSEEL at key anchor points for fixing the mesh (eg pubic tubercle in inguinal hernia repair) and at the margins of

the mesh. Application by spray, either alone or in combination with drops, should cover the mesh uniformly with a thin layer.

In inguinal hernia repair the mesh covering vascular structures and nerves can be fixed with TISSEEL alone using drops and/or spray.

### **Method of Preparation of TISSEEL Preloaded Syringe (Frozen)**

Thaw preloaded syringe in one of the three following options:

#### Option 1 – Thawing on the sterile field

33°C to 37°C sterile water bath: – transfer devices set and the inner pouch to the sterile field, remove devices set with preloaded syringes from inner pouch and place directly into sterile water bath. Ensure the contents of the syringe are completely immersed under the water.

Approximate thawing and warming times when using this method are:

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

#### Option 2 – Thawing off the sterile field

33°C to 37°C non-sterile water bath in two pouches: – maintain the devices set in both pouches and place into a water bath off the sterile field for appropriate time. Ensure the pouches remain submerged throughout thawing. Remove from the water bath after thawing, dry external pouch and transfer inner pouch and preloaded syringe onto the sterile field.

Approximate thawing and warming times when using this method are:

Pack Size	Thawing/Warming Times 33°C to 37°C Non-Sterile Water Bath (In Pouches)
2 mL	30 minutes
4 mL	40 minutes
10 mL	80 minutes

#### Option 3 – Thawing off the sterile field

Incubator (33°C to 37°C) in pouches: – maintain the devices set in both pouches and place into an incubator for appropriate time. Remove from incubator after thawing and transfer inner pouch and preloaded syringe onto the sterile field.

Approximate thawing and warming times when using this method are:

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

**Do not microwave TISSEEL.** TISSEEL should only be used when, after thawing, the Sealer Protein Solution has a viscous consistency similar to honey (air bubbles in the syringe chamber holding the Sealer Protein Solution slowly rise to the top when the double chamber syringe is tilted or turned upside down). If the Sealer Protein Solution has the consistency of a gel, it must be assumed to have become denatured due to an interruption of the cold storage chain. In this case, the fibrin sealant must not be used.

The protective syringe cap should not be removed until thawing is complete and application tip is ready to be attached. Do not use TISSEEL unless it is completely thawed and warmed (liquid consistency).

The solutions must be used within 72 hours after thawing at 25°C or below.

Any unused product and/or devices should be disposed of in accordance with local requirements.

### Method of Application

Application of TISSEEL must be completed within 4 hours after opening the preloaded frozen double chamber syringe. Discard any unused product. Separate, sequential application of the two components of TISSEEL must be avoided.

Prior to application, TISSEEL must be warmed to 33 – 37°C and must not be exposed to temperatures above 37°C.

Before application, the surface of the wound should be dried as much as possible. If application is interrupted, clogging occurs immediately in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the aperture of the joining piece (Y connector) facing the cannula is clogged, use the spare joining piece provided in the package.

To prevent TISSEEL from adhering to gloves and instruments, wet these with sodium chloride solution before contact.

In cases where very small volumes (1 to 2 drops) of TISSEEL are administered, expel and discard the first several drops from the application cannula immediately before application, to ensure adequate mixing of the sealer protein and thrombin solutions.

Caution must be used when applying fibrin sealant using pressurized gas.

- Any application of pressurized gas is associated with a potential risk of air embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening.
- TISSEEL with the spray set must not be used in enclosed body areas.
- TISSEEL must be sprayed only onto application sites that are visible.
- The user must follow the instructions and precautions in the device user manual, for example regarding the need to limit the gas pressure to a maximum of 2 bars. Do not spray closer than the distance recommended by the spray device manufacturer. The user is cautioned against the spray application of TISSEEL with devices produced by other manufacturers.

When spraying TISSEEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO<sub>2</sub> should be monitored because of the possibility of occurrence of air or gas embolism.

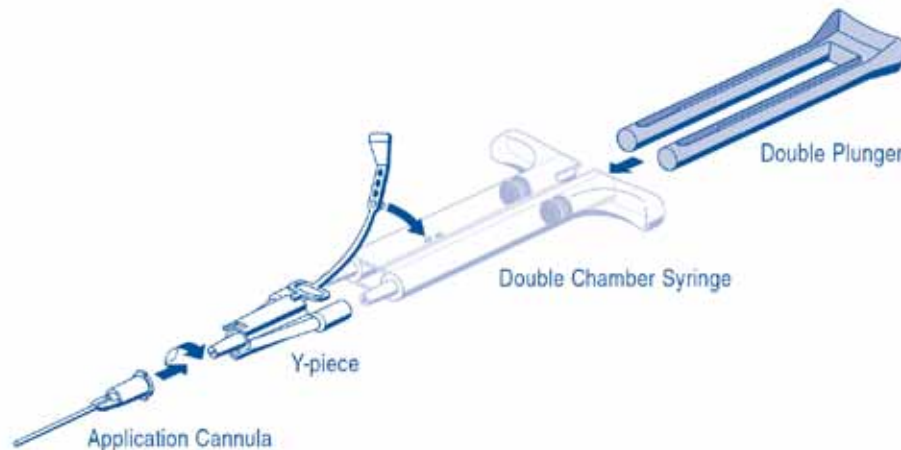
Application beyond the intended area of application should be avoided.

After the two components have been applied, fix or hold the sealed parts in the desired position for at least three to five minutes to ensure the setting TISSEEL adheres firmly to the surrounding tissue.

It is strongly recommended that every time TISSEEL is applied to a 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.

### **Operating Instructions**

For application, connect the double chamber syringe with the Sealer Protein Solution and the Thrombin Solution to a Y-piece and an application cannula (see diagram below) as provided in the accompanying set of devices. The double plunger of the double chamber syringe ensures that the equal volumes are fed through the Y-piece before being mixed in the application cannula and ejected.



Device Set Instructions: firmly connect the double chamber syringe nozzles to the Y-piece and secure it by fastening the tether strap to the syringe. Fit an application cannula onto the Y-piece. To avoid clogging, do not expel the air remaining inside the Y-piece or application cannula until application.

### **Incompatibilities**

Sealer Protein and Thrombin Solutions are denatured following contact with solutions containing alcohol, iodine or heavy metals. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of TISSEEL.

Oxidised cellulose-containing preparations may reduce the efficacy of TISSEEL and should not be used as carrier materials.

TISSEEL must not be mixed with other medicinal products.

### **OVERDOSAGE**

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. In the event of overdosage, please contact the Poison Information Centre at Phone Number: 131126.

### **PRESENTATION AND STORAGE CONDITIONS**

#### **Nature and Contents of Container**

##### Nature of containers:

Both Sealer Protein Solution and Thrombin Solution are contained in two separate chambers of a single use double chamber syringe made of polypropylene.

##### Contents:

Each pack TISSEEL contains

- One single use double chamber syringe, each chamber containing:



- Chamber number [1]: Sealer Protein Solution (with aprotinin) deep frozen
- Chamber number [2]: Thrombin Solution (with calcium chloride) deep frozen
- One set of devices (see below)

TISSEEL is available in the following pack sizes:

- TISSEEL, 2.0 mL (containing 1.0 mL of Sealer Protein Solution and 1.0 mL of Thrombin Solution)
- TISSEEL, 4.0 mL (containing 2.0 mL of Sealer Protein Solution and 2.0 mL of Thrombin Solution)
- TISSEEL, 10.0 mL (containing 5.0 mL of Sealer Protein Solution and 5.0 mL of Thrombin Solution)

See Table 2 below for details of active ingredients.

**Table 2: List of active ingredients and associated quantities**

	Sealer Protein Solution	Quantity	Thrombin Solution	Quantity
Active Ingredient	- Aprotinin (synthetic)	2250 KIU/mL	- Thrombin (human)	400 IU/mL
	- Factor XIII	1.2 IU/mL	- Calcium chloride (2 H <sub>2</sub> O)	36 micromole/mL
	- Fibrinogen	72 mg/mL		

### Shelf Life

Deep frozen TISSEEL has a shelf life of two years at temperatures < -18°C. The expiry date is stated on the final container and the package. Unopened pouches, thawed at 25°C or below, may be stored for up to 72 hours at 25°C or below after removal from the freezer.

If the product is removed from original pouch or warmed to 33-37°C, it must be used within 12 hours.

The TISSEEL solutions contain no antimicrobial agent. TISSEEL is intended for single use in one patient only and unused solution in the syringe should be discarded.

### Special Precautions for Storage

After thawing, the solutions must not be refrozen or refrigerated!

Store in a freezer (**at -18°C or colder**). The cold storage chain must not be interrupted until use.

Keep container in the outer carton to protect from light.

**Keep out of reach and sight of children.**

**For single use only. Do not re-sterilise!**

### **Set of Devices**

Each pack TISSEEL contains a double-sterile set of devices (DUO SET) consisting of one syringe double-plunger, two Y-pieces and four application cannulas. These devices are used for the simultaneous application of the fibrin sealant components. For details on application and complications associated therewith see DOSAGE AND ADMINISTRATION section, heading Operating Instructions using double-chamber syringe, double-plunger, Y-Piece and application cannulas.

The set of devices is sterile and non-pyrogenic in unopened and undamaged package. Sterilised by exposure to ethylene oxide.

### **NAME AND ADDRESS OF THE SPONSOR**

TISSEEL, Two-component Fibrin Sealant, deep frozen, Vapour Heated (VH) and Solvent Detergent (S/D) treated, is manufactured by Baxter AG, Vienna, Austria, and supplied in Australia by:

Baxter Healthcare Pty Ltd  
1 Baxter Drive  
Old Toongabbie, NSW 2146. Ph: 9848 1111, Fax: 9848 1123

### **POISON SCHEDULE OF THE MEDICINE**

Unscheduled

### **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

09 February 2009

### **DATE OF MOST RECENT AMENDMENT**

25 January 2012

TISSEEL, and DUO SET are trademarks of BAXTER AG. BAXTER is a trademark of Baxter International Inc.