Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Human fibrinogen / Human thrombin

Proprietary Product Name: VeraSeal

Sponsor: Grifols Australia Pty Ltd

June 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate transaminase
CI	Confidence interval
CMI	Consumer Medicines Information
CPD	Certified Product Details
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
FS	Fibrin Sealant
GMP	Good Manufacturing Practice
IFU	Instruction for Use
GVP	Good Pharmacovigilance Practices
INR	International normalised ratio
ITT	Intent(ion) to-treat
PDF	Portable document format
PI	Product Information
Ph. Eur	European Pharmacopoeia

Abbreviation	Meaning
PMF	Plasma master file (European Union)
PP	Per-protocol
PSUR	Periodic safety update report
RMP	Risk management plan
RR	Risk ratio
SAE	Serious adverse reaction
SE	Standard error
$T_{4/5/7/10}$	Haemostatic assessment at 4/5/7/10 minutes following time of start of initial study treatment (Fibrin Sealant Grifols, Surgicel, or manual compression) application
TBS	Target bleeding site
$T_{closure}$	Time of completion of the surgical closure by layers of the exposed surgical field containing the target bleeding site
$T_{completion}$	Time of end of initial Fibrin Sealant Grifols application before clamp release
TEAE	Treatment-emergent adverse event
TGO 88	Therapeutic Goods Order Number 88
T_{start}	Time of start of initial study treatment (Fibrin Sealant Grifols, Surgicel, or manual compression) application
TTH	Time to haemostasis
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	VeraSeal
Active ingredients:	Human fibrinogen / human thrombin
Decision:	Approved
Date of decision:	29 October 2021
Date of entry onto ARTG:	2 and 3 November 2021
ARTG numbers:	335950, 336835, 336836, 336837
, *Black Triangle Scheme:*[1]	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Grifols Australia Pty Ltd 5/80 Fairbank Road Clayton South, VIC, 3169
Dose form:	Solutions for sealant
Strengths:	80 mg/mL human fibrinogen and 500 IU/mL human thrombin
Container:	Syringe
Pack sizes:	2 mL (1mL human fibrinogen and 1mL human thrombin) 4 mL (2mL of human fibrinogen and 2mL human thrombin) 6 mL (3mL human fibrinogen and 3mL human thrombin) 10 mL (5mL human fibrinogen and 5mL human thrombin)
Approved therapeutic use:	*VeraSeal is used as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of hemostasis.*
Route of administration:	Epilesional
Dosage:	The use of VeraSeal is restricted to experienced surgeons who have been trained in the use of this medicinal product.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

The volume of VeraSeal to be applied and the frequency of application should always be oriented towards the underlying clinical needs for the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualised by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.3 to 12 mL. For other procedures, larger volumes may be required.

The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

Paediatric population:

The safety and efficacy of VeraSeal in children aged 0 to 18 years has not yet been established. Currently available data are described in Section 5.1 of the Product Information, but no recommendation on a posology can be made.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Grifols Australia Pty Ltd (the sponsor) to register VeraSeal (human fibrinogen / human thrombin) 80 mg/mL human fibrinogen and 500 IU/mL human thrombin, solutions for sealant for the following proposed indication:

> *VeraSeal is used as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of haemostasis. In addition, VeraSeal is indicated for suture support in vascular surgery.*

VeraSeal is effective in heparinized patients.

The human fibrin adhesion system constitutes the last phase of the physiological blood coagulation system leading to the formation of a semi-rigid fibrin clot. Fibrinogen, the main structural protein in the blood responsible for forming clots, is proteolytically cleaved and converted into fibrin monomers by thrombin. The fibrin monomers then polymerise to form insoluble fibrin. Thrombin also activates endogenous factor XIII, which catalyses the formation of covalent bonds between molecules of fibrin to form a cross linked clot capable of resisting dissolution. The fibrin clot also adheres to a variety of proteins, such as collagen, fibronectin, von Willebrand factor, and cell surface receptors, contributing to anchoring the clot to the injured site.

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledges, and/or electrocautery. Absorbable haemostatic agents such as bovine gelatine power and sponges, and haemostatic agents made from bovine collagen and oxidized cellulose are also used for stopping bleeding. Additionally, products containing thrombin and/or fibrinogen are used to assist body´s natural clotting mechanism to achieved haemostasis.

The intended benefits of fibrin sealant application are to support local haemostasis and sutures, 'glue' surfaces of injured tissues in order to obtain adaptation or sealing of surfaces, improve repair or healing. Fibrin sealant products may be used in a variety of clinical situations and surgical fields, including but not limited to, cardiac and vascular surgery, thoracic surgery, neurosurgery, plastic and reconstruction surgery, gastrointestinal surgery, hepatic and splenic surgery, and dental surgery. Practical applications of fibrin sealant products in orthopaedic surgery, interventional radiology and minimally invasive endoscopy are growing.

Fibrin Sealant Grifols (also known as 'VeraSeal' in this submission) is a medical device combination product consisting of a two component solutions of human fibrinogen and human thrombin with calcium chloride; supplied in separate pre-filled syringes assembled on a syringe holder and a plunger link, and co-packaged with an applicator tip (dual applicator). The dual applicator allows the simultaneous administration of equal amounts of fibrinogen and thrombin solutions by dripping or spraying without the requirement for the assistance of compressed gas. Of note, the 'dual applicator' was previously named 'airless spray accessory'. The single use kit is also supplied with two additional airless spray tips for spraying application.

Fibrin Sealant Grifols is intended as an adjunct to haemostasis for local administration to surgical sites, in situations where haemostatic measures based on conventional surgical techniques, such as suture, ligature, or cautery, are ineffective or impractical and as suture support in vascular surgery.

The dose regimen corresponds to a sufficient volume of Fibrin Sealant Grifols applied by dripping or spraying in order to entirely cover the intended surface area by a thin (1 mm thick), even layer. The application can be repeated if necessary, due to incomplete haemostasis. In clinical trials, the individual dosages have typically ranged from 0.3 to 12 mL. Larger volumes may be required for surgical procedures other than those included in the clinical studies.

Tisseel;[2] and Evicel;[3] are both fibrin sealant products currently registered on the Australian Register of Therapeutic Goods (ARTG). Both are derived from pooled human plasma and contain the same active ingredients as Fibrin Sealant Grifols. Tisseel also contains factor XIII and aprotinin, which has been associated with anaphylaxis.

[2] Tisseel was first registered on the ARTG on 13 March 2009 (ARTG number: 147141).
[3] Evicel was first registered on the ARTG on 22 October 2012 (ARTG numbers: 181318 and 181319).

This application was evaluated as part of the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium,[4] with work-sharing between the TGA, Health Canada, Swissmedic (Switzerland). Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA) on 1 November 2017, European Union (EU) on 10 November 2017, Canada on 25 March 2021, Singapore on 1 April 2021 and Switzerland on 20 May 2021. Similar applications were under consideration in Brazil (Submitted on 5 August 2020) and Israel (submitted on 4 January 2021).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	4 November 2016	Approved on 1 November 2017	*VistaSeal is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VistaSeal is effective in heparinized patients.*
European Union	28 November 2016	Approved on 10 November 2017	*Supportive treatment in adults where standard surgical techniques are insufficient:* *for improvement of haemostasis; as suture support: in vascular surgery.*
Canada	30 April 2020	Approved on 25 March 2021	*VistaSeal is indicated in adults for supportive treatment in surgery for improvement of hemostasis, and for suture support in vascular surgery, where standard techniques are insufficient.*

[4] The **Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium** is a medium-sized coalition, which was formed in 2007 by 'like-minded' regulatory authorities to promote greater regulatory collaboration and alignment of regulatory requirements. Its goal is to maximise international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products. For further information visit: https://www.tga.gov.au/australia-canada-singapore-switzerland-united-kingdom-access-consortium.

Region	Submission date	Status	Approved indications
			VistaSeal is effective in heparinized patients.
Singapore	20 July 2020	Approved on 1 April 2021	*VeraSeal is indicated as supportive treatment in adults where standard surgical techniques are insufficient:* · *for improvement of haemostasis.* · *as suture support: in vascular surgery.*
Switzerland	1 May 2020	Approved on 20 May 2021	*VeraSeal is used as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of haemostasis. In addition, VeraSeal is indicated as suture support in vascular surgery.* *VeraSeal is effective in heparinized patients.*
Brazil	5 August 2020	Under consideration	Under consideration
Israel	4 January 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-01828-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	2 June 2020
First round evaluation completed	27 November 2020
Sponsor provides responses on questions raised in first round evaluation	9 February 2021
Second round evaluation completed	26 March 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	23 July 2021
Sponsor's pre-Advisory Committee response	10 September 2021
Advisory Committee meeting	30 September and 1 October 2021
Registration decision (Outcome)	29 October 2021
Completion of administrative activities and registration on the ARTG	2 and 3 November 2021
Number of working days from submission dossier acceptance to registration decision*	251

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

The quality evaluator had no objections to the approval of VeraSeal, provided the proposed conditions of registration are agreed to by the sponsor. Notably, the sponsor was required to address numerous issues during the first two rounds of evaluation, and a third round was needed before these issues were resolved to the satisfaction of the quality evaluator.

Manufacturing

The manufacturing site for this product is located in Barcelona, Spain, and has Good Manufacturing Practice (GMP)[5] clearance expiring on 31 December 2021. There were no outstanding issues regarding manufacturing.

Specifications

The quality evaluator has no outstanding issues pertaining to specifications.

Stability

There were no issues pertaining to stability of fibrinogen or thrombin drug substance and drug product. Submitted data are supportive of the proposed shelf life of 2 years when stored at ≤ -18°C and protected from light, and proposed storage conditions of 48 hours at 2°C to 8°C or 24 hours at room temperature (20°C to 25°C) before use.

Viral safety

The viral safety evaluation was reassuring in its conclusion that sufficient evidence has been provided to demonstrate that the risks related to adventitious agents in the manufacturing of VeraSeal have been managed to an acceptable level.

Biological medicines derived from plasma must be obtained from plasma which complies with the requirements of 'human plasma for fractionation'.[6] Compliance to European Pharmacopoeia (Ph. Eur.) 0853 was demonstrated in the plasma master file (PMF) for this product (Grifols Type I PMF), which was assessed separately and approved by the TGA on 5 February 2021.

The sponsor has provided the details of the donor deferral criteria used, which are equivalent to the requirements of Therapeutic Goods Order Number 88 (TGO 88).[7]

Conclusion

There are no objections to the registration of this product from sterility, endotoxin, container safety and viral safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of VeraSeal have been controlled to an acceptable level.

Quality related proposed conditions of registration

- Laboratory Testing & Compliance with Certified Product Details
  - All batches of VeraSeal supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing

[5] **Good Manufacturing Practice (GMP)** describes a set of principles and procedures that when followed helps ensure that therapeutic goods are of high quality.
[6] European Pharmacopoeia (Ph. Eur.) Monograph 0853.
[7] **Therapeutic Goods Order Number 88 (TGO 88)** described the standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products. For further information, visit the TGA website: https://www.tga.gov.au/therapeutic-goods-orders.

are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in portable document format (PDF), for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  The CPD should be emailed post approval to biochemistry.testing@health.gov.au as a single PDF document.

Nonclinical

The nonclinical data submitted in support of this application consisted of *in vitro* studies and *in vivo* animal studies. *In vitro* studies demonstrated that coagulation occurred within 5 seconds independent from the lot, fill volume, thawing temperature or storage up to 24 hours.

In *in vivo* pharmacology studies in hepatic (spray) and cardiovascular (drip administration) surgery in swine and minipigs, respectively, and vascular surgery in rabbits (drip administration), the fibrin sealant was well tolerated, did not change vital functions (cardiac, respiratory) and reduced surgical time, number of stitches and bleeding.

The pharmacological effects were similar to those of other marketed fibrin sealants.

The non-gas assisted device of the presented VeraSeal product performed similarly to the gas assisted device.

The nonclinical evaluator concluded:

Overall, the submitted non-clinical documentation is considered to be sufficient to support the approval of VeraSeal with the known active pharmaceutical ingredients fibrinogen and thrombin in the proposed indication. The pharmaco-toxicological profile is considered well established and was sufficiently characterised. The nonclinical data are appropriately described in the risk management plan (RMP) and in the information for healthcare professionals.

Clinical

The clinical dossier consisted of 3 Phase III studies: Study IG1101, Study IG1102, and Study IG1103.

Efficacy

Study IG1101

Study IG1101 was a prospective, single blinded, randomised, Phase III superiority study comparing the haemostatic efficacy of Fibrin Sealant Grifols with that of manual compression in peripheral vascular surgery. Eligible patients were adult and paediatric patients undergoing elective open peripheral vascular surgery, where a target bleeding site (TBS) requiring a topical haemostatic agent was identified by the investigator

(surgeon). Only patients with a TBS rated moderate intensity on the proximal anastomosis were enrolled. The study was conducted in two parts: a preliminary part (I) in which all patients were treated with Fibrin Sealant Grifols to familiarise the study teams with the application procedure; and a primary part (II) in which patients were randomised 2:1 to Fibrin Sealant Grifols or manual compression.

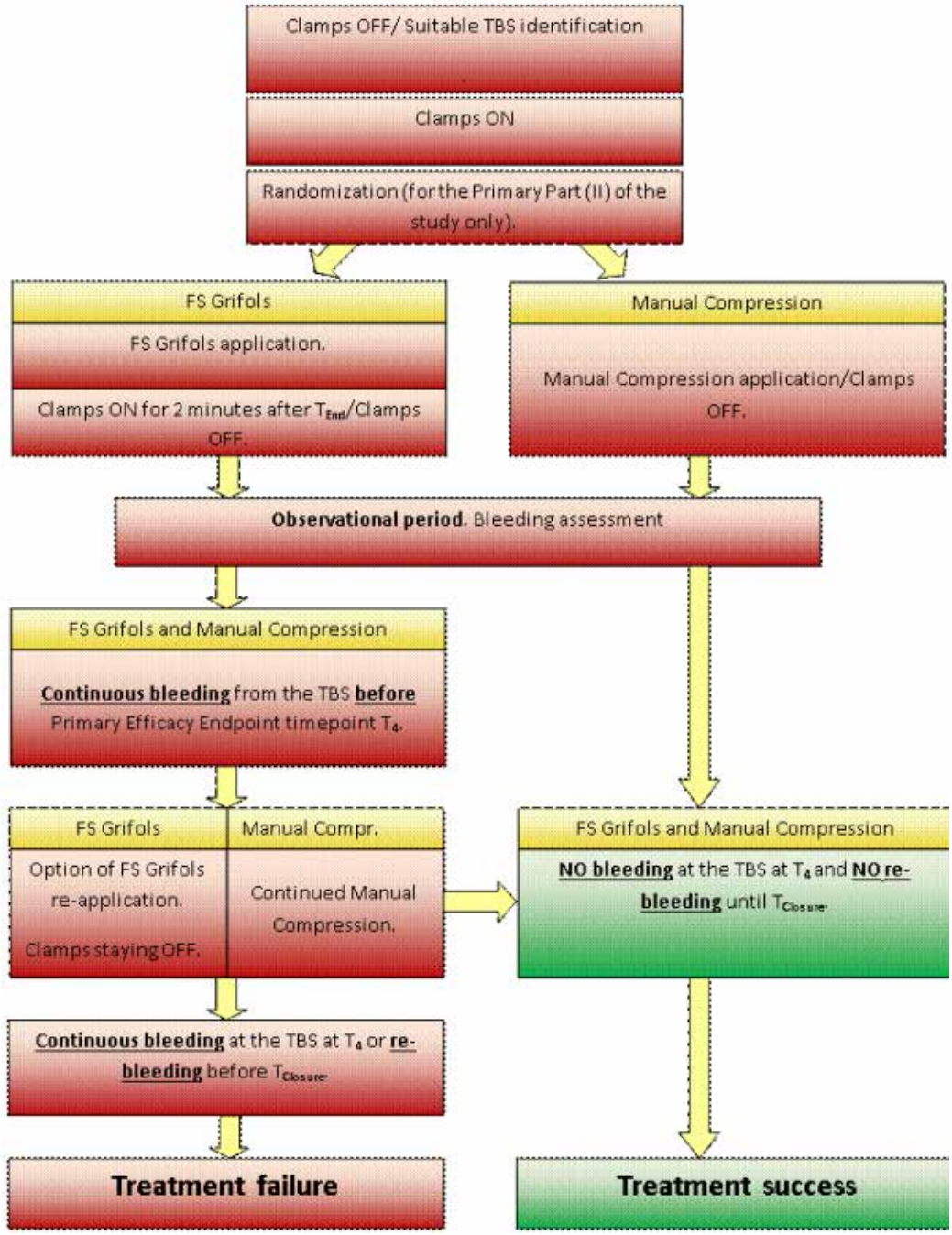
The surgical procedure was peripheral arterial bypass or upper extremity vascular access for haemodialysis (maximum 15% of patients). For the intervention group, 2 kits of 6 mL each of Fibrin Sealant Grifols were allocated for peripheral vascular procedures. Application of Fibrin Sealant Grifols was by dripping. Five applicator tips were made available for each patient. The control group received manual compression with gauzes/laparotomy pads normally available at the study centre.

The surgeon performed the surgical intervention according to his or her standards as well as the respective institution's standards. The use of polypropylene sutures (3-0, 4-0, 5-0 or 6-0) with 13 or 26 mm 3/8 or 1/2 circle taper point needles for the proximal anastomosis was required.

Anticoagulation with heparin before arterial clamping was required. Heparin reversal with protamine, if necessary, according to surgeon's judgment, was only allowed after the primary endpoint assessment at haemostatic assessment at 4 minutes following time of start of initial study treatment application (T_4).

The study design is shown in Figure 1 below.

Figure 1: Study IG1101 Diagram of study treatment application and primary efficacy endpoint assessment



FS = Fibrin Sealant; T_4 = haemostatic assessment at 4 minutes following time of start of initial study treatment (Fibrin Sealant Grifols, Surgicel, or manual compression) application; TBS = target bleeding site; $T_{closure}$ = time of completion of the surgical closure by layers of the exposed surgical field containing the target bleeding site.

Time to haemostasis (TTH) was measured in minutes at the start of treatment application (T_{start}), four minutes (T_4), five minutes (T_5), seven minutes (T_7) and ten minutes (T_{10}). The TTH was the time from T_{start} to the last effective haemostatic time point.

The primary efficacy endpoint was the proportion of patients in the primary part (Part II) of the study achieving haemostasis (yes/no) at the TBS by T_4 without occurrence of re-bleeding and reapplication of study treatment after T_4 and until surgical closure ($T_{closure}$), and without brisk bleeding and use of alternative haemostatic treatment after T_{start} and until $T_{closure}$.

Secondary efficacy variables included TTH, the proportion of patients achieving haemostasis at the TBS at T_5, T_7, and T_{10}, and the prevalence of treatment failures.

Safety variables included clinical safety, viral safety and immunogenicity.

In Part I of the study, 59 patients were enrolled. In Part II, 166 patients were randomised; 109 to Fibrin Sealant Grifols and 57 to manual compression. The rate of haemostasis by T_4 was 76.1% (83/109 patients) in the Fibrin Sealant Grifols treatment group and was 22.8% (13/57 patients) in the manual compression treatment group (risk ratio (RR) = 3.339 (95% confidence interval (CI): 2.047, 5.445, $p < 0.001$)). The mean TTH was 5.1 (± 0.21 standard error (SE)) in the Fibrin Sealant Grifols group and 8.2 (± 0.35 SE) in the manual compression treatment group. The rates of haemostasis at the TBS by T_5, T_7 and T_{10} were significantly higher in the Fibrin Sealant Grifols treatment group compared to the manual compression treatment group ($p < 0.001$), indicating that Fibrin Sealant Grifols was superior to manual compression.

In the Fibrin Sealant Grifols treatment group, the most common cause of treatment failure was persistent bleeding (22.9%, 25/109 patients). Of the 26 patients with treatment failure in the Fibrin Sealant Grifols treatment group, 96.2% (25/26) of the patients had persistent bleeding. In accordance with the protocol, no Fibrin Sealant Grifols-treated patients had treatment re-applied after T_4 and before $T_{closure}$.

In the manual compression treatment group, the most common causes of treatment failure were persistent bleeding (77.2%, 44/57 patients) and re-applied treatment after T_4 and before $T_{closure}$ (42.1%, 24/57 patients). Of the 44 patients with treatment failure in the manual compression treatment group, 44/44 (100.0%) patients had persistent bleeding.

Subgroup analyses of efficacy for the types of vascular surgeries were inconclusive due to insufficient number of patients per types of vascular surgeries within each treatment group.

Study IG1102

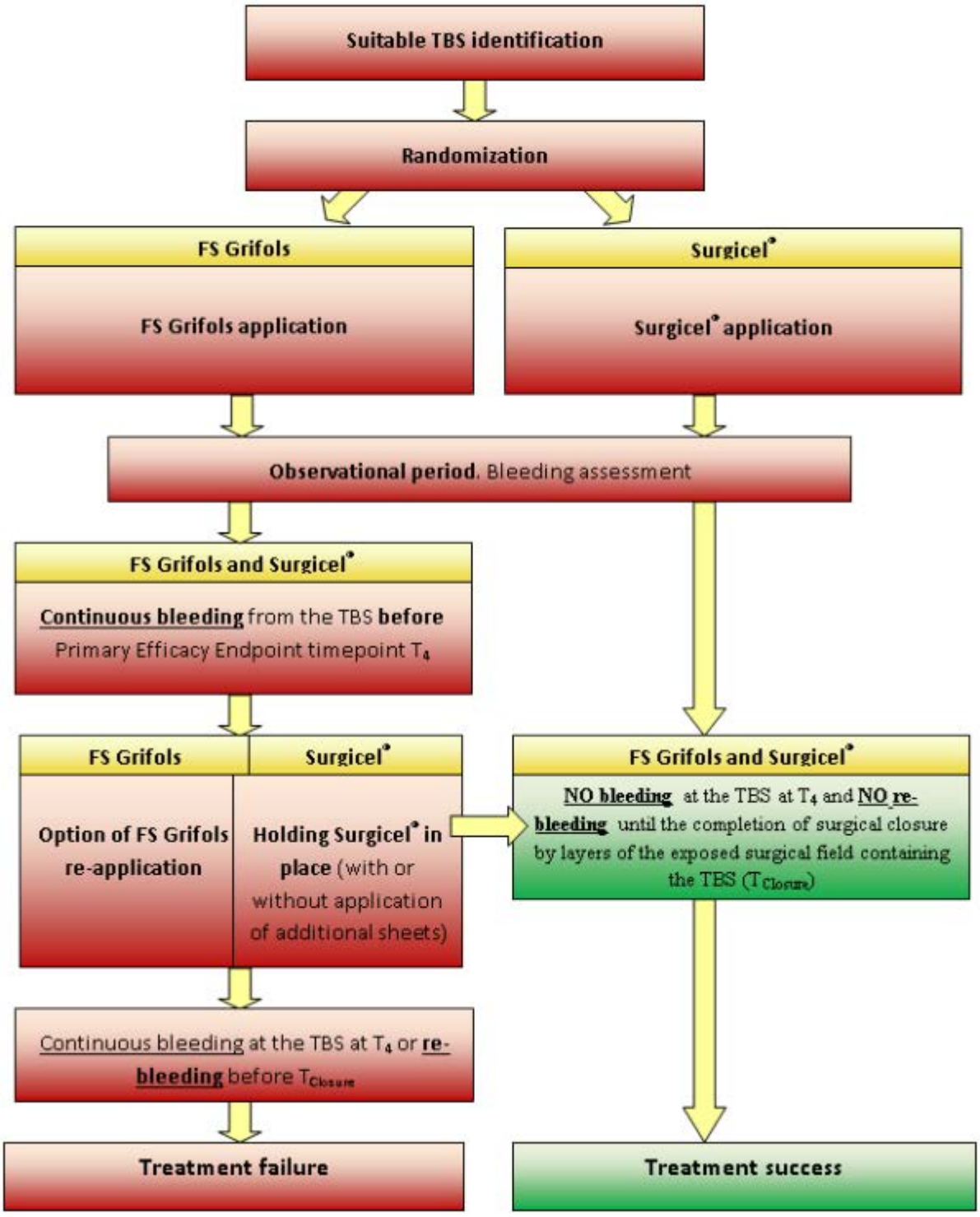
Study IG1102 was a prospective, single-blinded, randomised, Phase III non-inferiority study comparing Fibrin Sealant Grifols with a commercially available oxidised regenerated cellulose product Surgicel,[8] in parenchymous tissue open surgeries. Surgicel is currently registered on the ARTG (177702, 171589). Eligible patients were adult and paediatric patients undergoing elective open parenchymous tissue surgery of the liver, where a TBS requiring a topical haemostatic agent was identified by the investigator (surgeon).

The surgical procedure was elective, open hepatic resection (wedge or anatomic resections of a least one anatomical hepatic segment, or equivalent tissue volume) procedure. Application of Fibrin Sealant Grifols was by spraying with the assistance of gas pressure.

Again, this study was in two parts: the preliminary part (I) randomised patients 1:1 to Fibrin Sealant Grifols or Surgicel to allow study teams to familiarise themselves with the product. In the primary part (II), patients were also randomised 1:1 to Fibrin Sealant Grifols or Surgicel. The study design is shown in Figure 2 below.

[8] Surgicel was first registered on the ARTG on 21 October 2009 (ARTG number: 166221).

Figure 2: Study IG1102 Diagram of study treatment application and primary efficacy endpoint assessment



FS = Fibrin Sealant; T_4 = haemostatic assessment at 4 minutes following time of start of initial study treatment (Fibrin Sealant Grifols, Surgicel, or manual compression) application; TBS = target bleeding site; $T_{closure}$ = time of completion of the surgical closure by layers of the exposed surgical field containing the target bleeding site.

The primary efficacy variable was the proportion of patients in the primary part (II) of the study achieving haemostasis (yes/no) at the TBS by T_4 without occurrence of re-bleeding and re-application of study treatment after T_4 and until $T_{closure}$, and without brisk bleeding and use of alternative haemostatic treatment after T_{start} and until $T_{closure}$.

Secondary efficacy endpoints included TTH, the proportion of patients achieving haemostasis at other time points, and prevalence of treatment failures.

In the statistical analysis plan, it was determined that Fibrin Sealant Grifols would be deemed non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8. If non-inferiority was established, superiority may have been additionally claimed if the 95% CI was entirely above one.

One hundred and one (101) patients were enrolled in the preliminary part (I) intent-to-treat (ITT)[9] population, 52 of 101 patients were randomised to Fibrin Sealant Grifols, and 49 of 101 patients were randomised to Surgicel.

In the primary part there were 224 patients in the ITT population, 111 in the Fibrin Sealant Grifols group and 113 in the Surgicel group. The per-protocol (PP)[10] population in the Fibrin Sealant Grifols treatment group included 87 (87/111, 78.4%) patients, with twenty-four (24/111, 21.6%) patients having at least one major protocol deviation that might have an impact on the primary efficacy assessment were excluded from the PP population. The PP population in the Surgicel treatment group included 100 (100/113, 88.5%), with thirteen (13/113, 11.5%) patients having at least one major protocol deviation that might have an impact on the primary efficacy assessment were excluded from the PP population.

In the ITT population, the rate of haemostasis by T_4 was 92.8% (103/111 patients) in the Fibrin Sealant Grifols treatment group and was 80.5% (91/113) in the Surgicel group (RR = 1.152, 95% CI: 1.038, 1.279, p = 0.10). Fibrin Sealant Grifols was non-inferior to Surgicel and in addition, the lower limit of the 95% CI is above one, indicating that Fibrin Sealant Grifols was superior to Surgicel. In the PP population, the rate of haemostasis by T_4 was 98.9% (86/87 patients) in the Fibrin Sealant Grifols treatment group and 85.0% (85/100 patients) in the Surgicel treatment group (RR = 1.163, 95% CI: 1.068. 1.267, $p < 0.001$).

In terms of secondary endpoints, the rate of haemostasis by T_3 in the ITT population of the primary part (II) of the study was 85.6% (95/111) in the Fibrin Sealant Grifols treatment group compared to 62.8% (71/113) in the Surgicel group (RR = 1.362, 95% CI: 1.160, 1.600, $p < 0.001$). The median TTH was statistically and significantly shorter ($p < 0.001$) in the Fibrin Sealant Grifols treatment group (2.0 minutes) compared to the Surgicel treatment group (3.0 minutes). The rates of haemostasis by T_2, T_5 and T_7 were higher and statistically superior in the Fibrin Sealant Grifols treatment groups compared to the Surgicel treatment groups. By T_{10}, both Fibrin Sealant Grifols and Surgicel had similar rates of haemostasis. The estimated ratio of proportion of treatment failure in patients receiving Fibrin Sealant Grifols relative to Surgicel was 0.370 (0.172, 0.796, p = 0.010).

Subgroup analyses of efficacy by the size of the TBS suggest similar efficacy between treatment groups for large (> 100 cm^2) bleeding surfaces although sample size was too small to conclude.

Study IG1103

This was a prospective, single blinded, randomised, non-inferiority Phase III study comparing Fibrin Sealant Grifols with Surgicel during soft tissue open surgeries. The study design and duration were identical to Study IG1102. Adult and paediatric patients

[9] Randomised clinical trials analysed by the **intent-to-treat (ITT)** approach provide the unbiased comparisons among the treatment groups. In the ITT population, none of the patients are excluded and the patients are analysed according to the randomisation scheme.
[10] The **per-protocol (PP)** analysis is restricted to the participants who strictly adhered to the protocol. Also known as 'on-treatment' analysis.

undergoing urologic, gynaecologic, or general surgery procedures were eligible. Primary and secondary efficacy variables were the same as for Study IG1102.

The following elective, open surgical procedures were included:

- Simple or radical nephrectomies
- Total adrenalectomies
- Radical prostatectomies
- Pyeloplasties
- Radical cystectomies
- Simple or radical hysterectomies
- Lymphadenectomies were permitted in the retroperitoneal or pelvic region, only
- Retroperitoneal tumour resections. Additional soft tissue surgical types beyond the retroperitoneal and pelvic regions were permitted, resulting in the inclusion of mastopexies and abdominoplasties. The percentage of subjects enrolled with mastopexies and abdominoplasties could not have been > 35% in the primary part (II) of the study.

Application of Fibrin Sealant Grifols was by dripping and/or spraying with gas pressure assistance.

In the preliminary part of the study (I), the ITT population consisted of 103 patients; 51 randomised to Fibrin Sealant Grifols and 52 to Surgicel. In the primary part (II), there were 224 patients in the ITT population, 116 randomised to Fibrin Sealant Grifols and 108 to Surgicel. The PP population of the Fibrin Sealant Grifols group included 104/116 (89.7%) patients. The PP population in the Surgicel group included 102/108 (94.4%) patients.

In the ITT population, the rate of haemostasis by T_4 was 82.8% (96/116 patients) in the Fibrin Sealant Grifols treatment group and was 77.8% (84/108 patients) in the Surgicel treatment group (RR = 1.064, 95% CI: 0.934, 1.213, p = 0.401). In the PP population, the primary efficacy endpoint of haemostasis by T_4 was also achieved by 87/104 (83.7%) patients in the Fibrin Sealant Grifols group and 78/102 (76.5%) in the Surgicel group (RR = 1.094, 95%CI: 0.954, 1.255, p = 0.224).

The rate of haemostasis in the ITT population of the primary part (II) of the study was significantly higher (p = 0.015) in the Fibrin Sealant Grifols treatment group (75.9%, 88/116 patients) compared to the Surgicel treatment group (60.2%, 65/108 patients) only at T_3. Inferential analyses of the ratio and 95% CI of proportion of patients achieving haemostasis at the TBS by T_3 in patients receiving Fibrin Sealant Grifols relative to Surgicel was 1.260 (1.048, 1.516), indicating that Fibrin Sealant Grifols was superior to Surgicel at T_3.

The median TTH was 2.0 minutes in the Fibrin Sealant Grifols treatment group and 3.0 minutes in the Surgicel treatment group, but not significantly different (p = 0.06). Inferential analyses of the ratio and 95% CI of proportion of patients achieving haemostasis at the TBS by T_2, T_5, T_7, and T_{10} in patients receiving Fibrin Sealant Grifols relative to Surgicel indicated that Fibrin Sealant Grifols was non-inferior to Surgicel. The rates of haemostasis were not statistically different between treatment groups at all time points. The rate of treatment failure was lower, but not statistically significant in the Fibrin Sealant Grifols treatment group (20/116 (17.2%)) compared to the Surgicel treatment group (24/108 (22.2%)), RR = 0.776, 95%CI: 0.456, 1.321, p=0.401).

Subgroup analyses of efficacy by the size of the TBS suggest similar efficacy between treatment groups for large (> 100 cm^2) and medium (> 10 cm^2 and ≤ 100 cm^2) size

bleeding surfaces, but with a higher proportion of small (≤ 10 cm^2) bleeding surfaces achieving haemostasis in the Fibrin Sealant Grifols (85.2%) versus Surgicel group (74%). Sub-analysis by surgical procedure was inconclusive due to insufficient sample size for each type of surgery.

Integrated summary of efficacy

The sponsor provided an integrated analysis of Studies IG1102 and IG1103. Study IG1101 was excluded due to differences in the study design and surgical procedure. The integrated analysis showed a statistically significant difference between the rate of haemostasis at the TBS by T_4 in the Fibrin Sealant Grifols (87.7% (199/227 subjects)) and Surgicel (79.2% (175/221 subjects)) treatment groups (RR = 1.109, 95%CI: 1.021, 1.205, p = 0.014)).

Safety

Study IG1101

In the peripheral vascular surgery Study IG1101, safety variables included clinical safety, viral safety and immunogenicity, as follows:

- adverse events (AEs), adverse drug reactions (ADRs), and serious adverse reactions (SAEs);
- vital signs (heart rate, respiration rate, systolic and diastolic blood pressure, and temperature);
- physical assessments (classified physical abnormalities as clinically relevant or not);
- laboratory tests (serum clinical chemistry, complete blood count, coagulation panel (prothrombin international normalised ratio (INR), activated partial thromboplastin time (aPTT) ratio);
- viral panel: hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus type 1 and 2, and parvovirus B19;
- immunogenicity panel: antibodies against human factor V, human thrombin and human fibrinogen. The testing for antibodies would be necessary under the following conditions: inexplicable INR ≥ 2.0, or aPTT ratio ≥ 1.5 at postoperative Day 14 or Week 6.

Safety assessments were made at the following time points: screening visit, baseline visit, surgical procedure (Day 0; within 6 hours after surgical incision closure ($T_{completion}$)), post-operation Day 2 (± 1 day), Day 7 (± 1 day), Day 14 (± 2 days), Week 6 (± 4 days) and Month 3 (± 7 days). Study duration was approximately 4 months from the screening visit to the last viral safety follow-up at the Month 3 visit.

Summary of adverse events

The pooled safety population for Fibrin Sealant Grifols consisted of 168 patients (Part I and II combined). The following comments are based on the pooled safety population. Treatment-emergent adverse events (TEAEs) were similar between Fibrin Sealant Grifols pooled safety population (139/168 patients, 81.0%) and manual compression (44/57 patients 77.2%) treatment groups. None of the patients had an AE leading to study withdrawal.

Treatment-emergent SAEs were reported for 34 (20.2%) Fibrin Sealant Grifols patients and 11 (19.3%) manual compression patients. Most SAEs were considered unrelated to study treatment, except 2 cases of post-operative wound infection in the Fibrin Sealant Grifols group that were considered 'unlikely' related to study treatment, and one case of cellulitis also in the Fibrin Sealant Grifols group considered 'possibly' related. One case of

sepsis in the manual compression group was considered possibly related. There were 4 SAEs with the outcome of death in Fibrin Sealant Grifols group (myocardial infarction, gastrointestinal haemorrhage, multi-organ failure, and cause unknown) and none in the manual compression group. The 4 SAEs leading to death were considered not related to study treatment and started several days to weeks after surgery, except the case of multi-organ failure which started on Day 3.

Adverse drug reactions (ADRs) assessed as definitely, probably, possibly, or unlikely related to study treatment) were reported for 12.5% (21/168) of Fibrin Sealant Grifols patients and 5.3% (3/57) of manual compression patients. In the primary part (II) of the study, the incidence rates of ADRs were similar in the 2 treatment groups (7.3% in the Fibrin Sealant Grifols group and 5.3% in the manual compression group). Adverse drug reactions (ADRs), assessed for causal relationship to study treatment by the investigator were reported for a higher proportion of Fibrin Sealant Grifols patients (21/168, 12.5%) compared to manual compression patients (3/57, 5.3%). Serious ADRs were reported for 4 (2.4%) Fibrin Sealant Grifols patients and one (1.8%) manual compression patient. None of the patients had an ADR attributable to the application technique. The majority of ADRs were reported by single patients within the treatment groups and most were considered unlikely related to study treatment. Only in the Fibrin Sealant Grifols treatment group were ADRs reported by more than one patient, including procedural pain (4/168 (2.4%) patients) and nausea, pyrexia, vascular graft complication, parvovirus B19 test positive, and urinary retention (2/168 (1.2%) patients each). In the Fibrin Sealant Grifols pooled safety population, 2 ADRs were considered possibly related to study treatment: cellulitis and vascular graft complication (one patient each (0.6%)).

For the 2 patients with an ADR for parvovirus B19 antibody IgG detected, it was determined through additional evaluations (including scheduled and unscheduled testing) that there was no treatment-emergent infection with parvovirus B19.

No immunogenicity response was observed in patients treated with Fibrin Sealant Grifols or manual compression in the clinical study, demonstrating a comparable safety profile with respect to immunogenicity.

Study IG1102

Safety variables in this study were the same as for Study IG1101. The following relates to the pooled safety population which includes data from Parts I and II of Study IG1102.

Summary of adverse events

None of the patients had an AE leading to withdrawal.

Treatment-emergent adverse events (TEAEs) occurred in similar proportions in each treatment group (82.2% in Fibrin Sealant Grifols; 85.8% in Surgicel). SAEs were reported for 18.4% of Fibrin Sealant Grifols treated patients and 14.2% of Surgicel treated patients. SAEs in the Fibrin Sealant Grifols treatment group were mostly considered unrelated to study treatment except in 4 patients. All the SAEs in the 4 patients were considered ADRs unlikely related to study treatment, and include abscess, deep vein thrombosis (right femoral vein), deep vein thrombosis (left peroneal vein), and pulmonary embolism in one patient; deep vein thrombosis, post-procedural bile leak, and pulmonary embolism in one patient; liver abscess in one patient; and post-procedural bile leak in one patient. All of the SAEs in the Surgicel group were considered unrelated to study treatment. Ten deaths were reported during the study (7 Fibrin Sealant Grifols patients and 3 Surgicel patients). All of these were the outcome of AEs considered not related to study treatment.

Adverse drug reactions (ADRs) were reported for a higher proportion of Fibrin Sealant Grifols treated patients (11/163, 6.7%) compared to Surgicel treated patients (3/162, 1.9%). The majority of ADRs occurred in single patients within the treatment groups and most were considered unlikely related to study treatment. In the Fibrin Sealant Grifols

treatment group, one ADR (procedural pain) was considered definitely related to study treatment, and 3 ADRs (hyperthermia, contusion, and procedural pain) were considered possibly related to study treatment. In the Surgicel treatment group, 2 ADRs (procedural pain and pancreatitis) were considered possibly related to study treatment. No ADRs were attributed to the application technique.

Immunogenicity to Fibrin Sealant Grifols was not detected for antibodies to human factor V, human thrombin, and human fibrinogen. No treatment-emergent viral infection was detected by deoxyribonucleic acid or viral serology testing.

Study IG1103

The safety endpoints were the same as for the previous studies, and the following refers to the pooled safety population consisting of patients in Parts I and II of Study IG1103.

Summary of adverse events

Although none of the patients had an AE leading to withdrawal, one patient withdrew from the study at Day 7 after being diagnosed with a deep vein thrombosis the day before.

Treatment-emergent adverse event (TEAE) rates were similar between treatment groups (88.2% in Fibrin Sealant Grifols; 88.0% in Surgicel, pooled safety population). SAEs were reported for 17/169 (10.1%) Fibrin Sealant Grifols treated patients and 18/158 (11.4%) Surgicel treated patients. SAEs in the Fibrin Sealant Grifols treatment group were considered unrelated to study treatment except for one patient with 2 SAEs of abdominal wound dehiscence and peritonitis, which were considered possibly related to the study treatment and also attributable to application technique. Three deaths were reported in the study (2 Fibrin Sealant Grifols patients and one Surgicel patient), all considered not related to treatment.

Adverse drug reactions (ADRs) were reported for a slightly greater proportion of Fibrin Sealant Grifols treated patients (32/169 (18.9%) patients) compared with Surgicel patients (24/158 (15.2%) patients). The majority of ADRs occurred in single patients. In the Fibrin Sealant Grifols group, exceptions were procedural pain, pruritus and nausea (occurred in 4 patients each (2.4%)); and, anaemia, insomnia, hypertension, leukocytosis, ileus, prothrombin time prolonged, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, hypocalcemia, hypokalemia, hyponatremia, and headache (2 patients each (1.2%)). In the Surgicel group, the exceptions were: anaemia and pyrexia (5 patients each (3.2%)); procedural pain (4 patients each (2.5%)), constipation (3 patients (1.9%)); and, anxiety, insomnia, wheezing, pruritus, and hypertension (2 patients each (1.3%)). Most ADRs were considered unrelated to treatment. In the Fibrin Sealant Grifols group, 8 ADRs were considered possibly related to study treatment, including pruritus, prothrombin time prolonged (2 patients), pyrexia, peritonitis, abdominal wound dehiscence, parvovirus B19 test positive (later attributed to blood transfusion), and somnolence.

In the Surgicel group, 9 ADRs were considered possibly related to study treatment, including procedural pain, anaemia (2), prothrombin time prolonged, pyrexia (3), vaginal cellulitis, white blood cell counts increased.

Immunogenicity to Fibrin Sealant Grifols was not detected for antibodies to human factor V, human thrombin, and human fibrinogen. No treatment-emergent viral infection was detected by DNA or viral serology testing.

Integrated summary of safety

The sponsor provided a summary containing integrated safety data from all three studies. The overseas regulator provided the following comments:

> *'In the integrated summary of safety, the incidence of TEAEs was mostly attributed to the surgical procedures or medical conditions of the patient. The 17 fatal cases*

reported in the three studies Fibrin Sealant Grifols 13/500 (2.6%) and Surgicel 4/320 (1.3%)) were not considered related to the study treatment. Overall, the summary of TEAEs suggest comparable surgical procedures and complications reported between the treatment groups. In contrast, the ADRs related to treatment application and study drug suggest an overall higher risk attributed to the use of FS [Fibrin Sealant] Grifols as compared to Surgicel. Patients receiving manual compression were under represented. The sponsor was requested to ensure that the ADR causality assessments included all ADRs irrespective of their degree of severity as well as taking into consideration those with a reasonable relation to the known risks with the use of a fibrin sealant, with or with assistance of gas pressure. In fact, there is a higher incidence of thrombi and infections in the FS Grifols group compared to Surgicel.

The risk of viral transmission with the use of FS Grifols was obscured by an unusually high frequency of false viral testing results, and the presumably explanation for positive test arising during the clinical trials attributed to tainted blood products. sponsor provided additional clarification about the cases of viral transmission during the clinical trials, which were considered related to the passive transfer of antibodies from blood components administered to the patients.'

Through additional questions and responses from the sponsor, all safety related concerns were resolved to the satisfaction of the clinical evaluator. Nevertheless, the known risks of thrombin sealants must be adequately mitigated by clear warnings in the PI.

Drug delivery device

There are two devices currently included on the ARTG for use with Fibrin Sealant Grifols. Both devices are Class IIa;[11] and were included in the ARTG without audit review. Essentially, the TGA assessed the application form and the quality management systems certificate, but there was no clinical or nonclinical evaluation of these devices. This is standard procedure for Class IIa devices. Both devices are CE;[12] marked and have Food and Drug Administration (FDA) 510k;[13,14] approval.

ARTG 322484

This device was included in the ARTG on 30 August 2019 as 'Johnson and Johnson Medical Pty Ltd - haematological concentrate/haemostatic agent cannula, open-surgery.' The intended purpose is '*a device intended to be used during a surgical procedure for the administration of a haemostatic agent to a bleeding surgical site, typically to facilitate haemostasis and healing*.' In the clinical trials, an equivalent device was used to administer Fibrin Sealant Grifols by dripping or by spraying with gas assistance. The overseas regulator drew the following conclusion about this device:

'Although FS Grifols kit has the potential to contribute to a patient harm, the benefits that it provides in bleeding control clearly outweigh the risks. During the risk

[11] Medical devices will be placed into one of the main classifications depending on the level of risk they pose. The higher classification level, the tougher the requirements will be. **Medical device Class IIa** poses low public health risk or moderate personal risk.
[12] The **CE mark** signifies compliance with European standards, as assessed by a notified body; device images In vivo distribution of radiopharmaceuticals in a patient; Device allows direct diagnosis or monitoring of vital physiological processes of a patient (does not indicate if patient is in immediate danger).
[13] Food and Drug Administration (FDA) **Section 510(k)** of the *Food, Drug and Cosmetic Act* requires device manufacturers who must register, to notify the FDA of their intent to market a medical device at least 90 days in advance. This allows FDA to determine whether the device is equivalent to a device already placed into one of the three classification categories.
[14] Demonstration of substantial equivalence with a registered device is sufficient for 510k approval.

analysis some mitigations have been specified and applied so as to reduce the risks to acceptable levels for the patient, by greatly lowering the probability.'

The overseas regulator's toxicology evaluation compared the device without gas assistance to the equivalent device with gas assistance and found that:

'The new device was at least as efficacious as the gas-assisted spray devices for both drip and spray administration.'

ARTG 322483

This device was included in the ARTG on 30 August 2019 as 'Johnson and Johnson Medical Pty Ltd - haemostatic-agent endotherapy cannula.' The intended purpose is '*a device intended to be used during a laparoscopic procedure to provide access for the administration of a haematological concentrate and/or haemostatic agent to a bleeding surgical site, typically to facilitate haemostasis and healing.*' This device was not used in the clinical trials, as there were no laparoscopic procedures included in the trials, therefore, evidence for this device in clinical use is lacking.

Risk management plan

The sponsor has submitted EU-RMP version 4.2 (dated 6 April 2020; data lock point (DLP) 8 June 2018) and Australia specific annex (ASA) version 1.0 (dated 11 March 2020) in support of this application. At the second round of evaluation, the sponsor submitted EU-RMP version 4.3 (dated 17 December 2020; DLP 8 June 2018) and ASA version 2.0 (dated 17 December 2020). At the third round of evaluation, the sponsor submitted EU-RMP version 4.1 (dates 21 October 2019; DLP 8 June 2018) and ASA version 3.0 (dated 12 April 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[15]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Thromboembolic events	ü	–	ü	–
	Transmission of infectious agents	ü	–	ü	–
	Medication error	ü	–	ü	ü†
Missing information	Use in pediatric patients under the age of 18	ü	ü*	ü	–

[15] *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.
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 labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Pregnant and breastfeeding women	ü	–	ü	–

* Paediatric investigation study (United States of America, Europe)

† Educational program for healthcare professionals

- At the first round of evaluation, no safety concerns were proposed. The sponsor was asked to include thromboembolic events, transmission of infections agents and medication error as important potential risks; and use in paediatric patients under the age of 18 and in pregnant and breastfeeding women as missing information in the summary of safety concerns. At the second round of evaluation, the sponsor added the requested safety concerns to the ASA. The summary of safety concerns is now acceptable from an RMP perspective.
- At the first round of evaluation, pharmacovigilance activities were not listed as there were no safety concerns proposed, however the sponsor was requested to include a paediatric investigation study, as agreed with the FDA and European Medicines Agency (EMA), as an additional pharmacovigilance activity for the recommended paediatric safety concern. At the second round of evaluation the paediatric investigation study has been added to the ASA as an additional pharmacovigilance activity. Although no Australian patients are to be included in this study, the results are considered relevant to the Australian population. The pharmacovigilance plan is acceptable.
- Routine and additional risk minimisation activities were not proposed at the first round of evaluation as no safety concerns were proposed. Additional risk minimisation activities, in the form of health care professional education, were recommended for the requested important potential risks of medication error, thromboembolic events and transmission of infectious agents. At the second round of evaluation, the sponsor proposes routine risk minimisation activities for all safety concerns. At the third round of evaluation, the sponsor agreed to add an educational program for surgeons to the risk minimisation plan as recommended. Revision of the Consumer Medicines Information (CMI) and the additional risk minimisation materials is required prior to marketing, however the risk minimisation plan is generally acceptable at the third round of evaluation.

Risk-benefit analysis

Delegate's considerations

The clinical evidence provided constitutes adequate evidence of the efficacy of Fibrin Sealant Grifols. The key issues with this submission relate to uncertainty regarding the breadth of procedures for which Fibrin Sealant Grifols is suitable, and safety concerns related to the application method and devices.

Indication

The proposed indication is broad and does not restrict use of Fibrin Sealant Grifols to particular types of surgical procedures. According to the indication, the product could be used for open or laparoscopic surgery at a range of anatomical sites. The PI does include the following limitations:

> *'Adequate data are not available to support the use of this product in tissue gluing, neurosurgery, application through a flexible endoscope for treatment of bleeding or in gastrointestinal anastomoses.'*

The 3 clinical studies provided in support of this application covered a limited range of open surgical procedures including peripheral vascular surgery, open parenchymous tissue surgery of the liver, and open urological, gynaecological, or general surgeries. There was no laparoscopic surgery included in the trials.

The broad indication proposed by the sponsor relies upon the extrapolation of clinical trial data from a limited number of procedures to a wider range of surgical procedures. While this may be appropriate for some procedures, the sponsor acknowledges in the PI that evidence is lacking for neurosurgery, endoscopy and tissue gluing. The extent to which the clinical trial data can be extrapolated to other surgical procedures is uncertain. Depending on the advice from the Advisory Committee on Medicines (ACM), it may be necessary to add further limitations to the indication and/or the PI.

Laparoscopic device

The 'haemostatic-agent endotherapy cannula' device currently included in the ARTG (322483) is intended to administer Fibrin Sealant Grifols during laparoscopic procedures. No clinical evidence to support this device, or the use of Fibrin Sealant Grifols in laparoscopic procedures has been provided to the TGA. Although the ARTG entry for this device does not include the name 'VeraSeal,' the Instructions for Use (IFU) provided to TGA with the device application labels the device 'VeraSeal laparoscopic dual applicator,' and the indication is '*to be used for the simultaneous topical application of the two biological components of VeraSeal solutions for sealant onto the surface.*' The device is clearly intended to be used with Fibrin Sealant Grifols. There is substantial uncertainty regarding the safety and efficacy of this device, and the safety and efficacy of the use of Fibrin Sealant Grifols in laparoscopic procedures.

Application method

In the clinical trials, there were restrictions on the application technique used. Fibrin Sealant Grifols had to be applied by dripping in vascular surgeries, and by spraying with gas assistance in other types of procedures. The PI provides instructions for application by dripping and by spraying, but does not specify which technique should be used for which procedures. Furthermore, the PI is silent on the use of gas assistance, implying but not explicitly stating that gas assistance is not necessary. The sponsor submitted some non-clinical evidence to suggest that application of Fibrin Sealant Grifols by spraying with gas assistance was at least as efficacious as spraying without gas assistance and drip application. The use of gas assistance for spray application of fibrin sealants may increase the potentially fatal risk of air or gas embolism. Therefore, it may be prudent to warn against the use of gas assistance in the PI.

Safety and the Product Information

There are several serious risks associated with the use of fibrin sealant products including air or gas embolism and other thromboembolic complications, infectious disease transmission, immunogenicity and allergy or anaphylaxis. In the clinical trials, the rates of ADRs were higher in the Fibrin Sealant Grifols groups compared to the control groups, including higher rates of infection and thromboembolic events. The proposed PI lists thromboembolic complications in the 'Special warnings and precautions' section, and has subheadings and text for hypersensitivity reactions and transmissible agents. The summary of the safety profile includes a sentence stating that antibodies against components of fibrin sealant or haemostatic products may occur rarely. These warnings are buried in the body of the PI, and are not immediately obvious on the first page of the PI. Notably, the Canadian PI contains a box warning which highlights the risk of

thromboembolic complications and infectious agents. The Delegate is suggesting a similar box warning should be added to the Australian PI, and the ACM's advice is sought on this.

Tradename

The proposed tradename for Australia is 'VeraSeal.' The TGA tradenames committee considered that 'Seal' was promotional as it implies that the product seals the wound. Of note, there is another similar product registered on the ARTG with the name 'Tisseel' (note the difference in spelling).

The overseas regulator raised the following issues with the 'Vera' part of the name, and ultimately rejected the name 'VeraSeal' for the following reasons:

> *'[The overseas regulator's] brand name review considers the proposed brand name 'VeraSeal' implies unique effectiveness and the product has a superior and better efficacy compared to other products in the same therapeutic class. The name exaggerates the product efficacy by implying it is the best sealant with the inclusion of the prefix 'Vera' similar to 'very'. In addition, 'Vera' in Latin means 'true', 'real' or 'genuine' that can relate VeraSeal to 'True Seal' in comparison with other products in same therapeutic class and can be interpreted a better product. VeraSeal interpreted as 'True Seal' may imply exaggerated efficacy in comparison with other products in same therapeutic class.'*

The sponsor's reply to the issues raised by the TGA tradenames committee states that the devices currently included on the ARTG are already labelled 'VeraSeal' and they are designed to be cross labelled with the medicinal product. Notably, ARTG summaries 322483 and 322484 do not contain the name 'VeraSeal,' however, the IFUs are labelled 'VeraSeal' and the indications in the IFUs specify that the device is for administration of 'VeraSeal solutions for sealant' despite this being an unregistered good at present.

The name 'VeraSeal' has been accepted in the EU and Switzerland; however the alternative name 'VistaSeal' was required by the FDA and Health Canada.

Proposed action

After three rounds of evaluation, most issues have been resolved to the satisfaction of the quality, nonclinical, and clinical evaluators. ACM advice is requested on the outstanding issues and their relevance in the Australian context.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please provide the Instructions for Use for all devices intended to be used to administer VeraSeal.***

The IFUs of VeraSeal Dual Applicator Assembly Guide and of VeraSeal Laparoscopic Dual Applicator Assembly Guide are provided to the TGA.

Advisory Committee considerations[16]

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

[16] The **ACM** provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

Specific advice to the Delegate

1. Should the indication be restricted to particular types of surgical procedures? If so, what should the restrictions be?

The ACM agreed that the indication should not be restricted to particular types of surgical procedures, commenting that the use of the product should be left to clinical discretion. Further discussion of the indication is included in the response to Question 6, below.

2. Is it appropriate to extrapolate the evidence for use of Fibrin Sealant Grifols [known as 'VeraSeal' in this application] in open surgery to laparoscopic surgery with the laparoscopic device?

The ACM considered it appropriate to extrapolate the evidence for use of Fibrin Sealant Grifols in open surgery to laparoscopic surgery with the laparoscopic device, as they were of the view that that the laparoscopic device/applicator will have similar safety and efficacy to the open surgery device, and to other similar devices on the ARTG. The ACM commented that it can be challenging to manage bleeding in laparoscopic surgery as pressure cannot be applied, therefore VeraSeal could have utility in laparoscopic surgery.

3. Is it necessary to specify a particular application technique for certain procedures? That is, dripping for vascular surgery?

The ACM was of the view that it is not necessary to specify a particular application technique for certain procedures as this would be adequately managed by the surgeon.

The ACM discussed that the application technique would only be a concern with a gas generated spray leading to a risk of gas embolism and were reassured that the sponsor has noted that gas assistance cannot be used with this product.

4. Does the risk of thromboembolic disease warrant a box warning in the Product Information? Are there other risks that should be included in the box warning or elsewhere in the Product Information?

The ACM agreed that the risk of thromboembolic disease was not a significant concern and that this risk does not warrant a box warning in the PI. In providing this advice, the ACM commented that the risk of thromboembolic disease is much higher from the surgical procedure itself.

The ACM did not raise any other substantive risks that need to be included in the PI.

5. Is the proposed tradename 'VeraSeal' acceptable for Australia?

The ACM noted the reasoning for approval of the alternative name 'VistaSeal' in Canada, and the view of the TGA tradenames committee, however the ACM did not have any significant concerns with the proposed Australian tradename of 'VeraSeal'.

6. The committee is invited to comment on any other issues it deems relevant to this submission.

The ACM advised that the most appropriate indication wording to reflect the use of the product is:

> *VeraSeal is used as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of haemostasis.*

The ACM was of the view that the additional proposed sentences, '*In addition, VeraSeal is indicated for suture support in vascular surgery. VeraSeal is effective in heparinized patients.*', were not necessary to include in the indication. In providing this advice, the ACM commented that inclusion of these two sentences could promote overutilisation of the product in settings where other products or techniques might be more appropriate. The ACM advised that vascular surgeons would be unlikely to use this product for suture support in vascular surgery.

The ACM noted that the sponsor has agreed to put a warning in the PI about the low potential risk of infectious disease transmission of parvovirus B19, Creutzfeldt-Jakob disease, and unknown pathogens. The ACM was supportive of the inclusion of this warning as the product is comprised of pooled human plasma. The ACM emphasised the importance of the batch number being recorded in the patient's medical records for tracing purposes in case of transmitted infection.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *VeraSeal is used as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of haemostasis.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of VeraSeal (human fibrinogen / human thrombin) 80 mg/mL human fibrinogen and 500 IU/mL human thrombin, solutions for sealant, syringe, indicated for:

> *VeraSeal is used as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of hemostasis.*

Specific conditions of registration applying to these goods

- VeraSeal (human fibrinogen / human thrombin) is to be included in the Black Triangle Scheme. The PI and CMI for VeraSeal must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The VeraSeal EU-risk management plan (RMP) (version 4.1, dated 21 October 2019, data lock point 8 June 2018), with Australian specific annex (version 3.0, dated 12 April 2021), included with Submission PM-2020-01828-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Additional conditions:

  All batches of VeraSeal supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results

<https://www.tga.gov.au/ws-labs-index> and periodically in testing reports on the TGA website.

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) <https://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

The CPD should be emailed post approval to biochemistry.testing@health.gov.au as a single PDF document.

Any changes to the VeraSeal fibrinogen manufacturing process post-approval that potentially result in further removal of endogenous fibrin stabilising factor XIII must be submitted to the TGA as a Category 3 application with justification (including supporting data) as to why the change will not affect product quality.

Attachment 1. Product Information

The PI for VeraSeal approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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