EU Risk Management Plan for VeraSeal®
[Fibrin Sealant (Fibrinogen (Human) / Thrombin (Human)]

RMP version to be assessed as part of this application:

RMP Version number: 7.0

Data lock point for this RMP: 30-Nov-2022

Date of final sign off: See left margin

Rationale for submitting an updated RMP: Corrections requested on Procedure No. EMEA/H/C/004446/II/0027: updates to reflect the approved indication in line with the inclusion of paediatric indication, avoiding use of reference to changes proposed but not approved.

Summary of significant changes in this RMP: Inclusion of paediatric indication reflected as approved

Other RMP versions under evaluation:

RMP Version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number: version 4.1

Approved with procedure: Centralized Procedure number EMEA/H/C/004446/II/0006/G

Date of approval (opinion date): 14-Nov-2019

QPPV name: Juan Oliveras

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Fibrinogen (Human)/ Thrombin (Human)
Pharmacotherapeutic group(s) (ATC Code)	B02BC
Marketing Authorisation Holder	Instituto Grifols, S.A. Can Guasch, 2 08150 Parets del Vallès Barcelona Spain
Medicinal products to which this RMP refers	Fibrin Sealant
Invented name(s)	VeraSeal®* *During the development and clinical trials phase the name of the product was FS Grifols. This name is used in the Risk Management Plan referring to the same product.
Marketing authorisation procedure	Centralized Procedure
Brief description of the product	Chemical class: Local haemostatics
	<u>Mechanism of action:</u> The human fibrin adhesion system initiates the last phase of 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 polymerize to form insoluble fibrin. Thrombin also activates factor XIII that catalyses the formation of covalent bonds between molecules of fibrin to form a cross-linked clot capable of resisting dissolution. The presence of Ca++ is required for most reactions that lead to the generation of active thrombin. The clot adheres to a variety of proteins, such as collagen, fibronectin, von Willebrand factor and cell surface receptors, contributing to anchoring the fibrin clot to the injured site. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated. Fibrin sealant/haemostatic products are metabolised in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

	<u>Important information about its composition:</u> VeraSeal® mainly consist of fibrinogen and thrombin with calcium chloride frozen solutions, which, when mixed, generate a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation system, and that may assist wound healing. Human fibrinogen, component of VeraSeal®, is obtained [redacted] on Cohn's method [redacted], obtained from human plasma. Human thrombin, component of VeraSeal®, is produced [redacted] according to the same procedure.
Hyperlink to the Product Information	See product information
Indication(s)	Current: VeraSeal® is indicated as a supportive treatment in adults and children where standard surgical techniques are insufficient: for improvement of haemostasis and as a suture support in vascular surgery.
	Proposed: Not applicable
Dosage	Current: For epilesional use. Dose to be applied is governed, 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 been evaluated in a clinical study. Currently available data are described in section 5.1. Application of the product must be individualised by the treating physician. In the paediatric clinical trial, the individual dose ranged from 0.6 to 12 mL
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	Current: Solutions for sealant. Frozen solutions. The product is supplied as a single-use kit containing two separate pre-filled syringes (glass type I) with rubber stoppers assembled on a syringe holder, each containing 1 ml, 2 ml, 3 ml or 5 ml solution of Human Fibrinogen and Human Thrombin, respectively. The content of Human fibrinogen is 80 mg/ml and the content of Human thrombin is 500 IU/ml.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indications:

VeraSeal® is indicated as a supportive treatment in adults and children where standard surgical techniques are insufficient: for improvement of haemostasis and as a suture support in vascular surgery.

Target population: The product is aimed to treat all population. However, there are limitations due to concomitant illnesses, known alcohol or drug abusers, and female subjects who are pregnant or nursing.

The product is limited also to patients who have an active infection in the anatomic surgical area, and subjects with an International Normalized Ratio (INR) > 2.5.

Incidence/ Prevalence:

Worldwide volume of surgery is large. In view of the high death and complication rates of major surgical procedures, surgical safety should now be a substantial global public-health concern. The disproportionate scarcity of surgical access in low-income settings suggests a large unaddressed disease burden worldwide. Public-health efforts and surveillance in surgery should be established. In a study which obtained surgical data for 56 (29%) of 192 WHO member states, they estimated that 234.2 (95% CI 187.2–281.2) million major surgical procedures are undertaken every year worldwide or approximately one operation annually for every 25 human beings alive [1,2].

Demographic profile:

Surgical approaches are receiving increasing attention as a way to solve many global public health problems. Data from the World Bank reported that in 2002, an estimated 164 million disability-adjusted life years, representing 11% of the entire disease burden, were attributable to surgically treatable conditions. Although surgical care can prevent loss of life or limb, it is also associated with a considerable risk of complications and death. Surgical complications are common and often preventable. The risk of complications is poorly characterized in many parts of the world, but studies in industrialized countries have shown a perioperative rate of death from inpatient surgery of 0.4 to 0.8% and a rate of major complications of 3 to 17%. These rates are likely to be much higher in developing countries. Data suggest that at least half of all surgical complications are avoidable. Efforts to implement practices designed to reduce surgical site infections, management of blood loss or anesthesia-related mishaps have been shown to reduce complications significantly. Thus, surgical care and its attendant complications represent a substantial burden of disease worthy of attention from the public health community worldwide.

Some procedures, such as major vascular surgery, inevitably involve heavy blood loss. Other circumstances can also predispose a patient to unusually heavy bleeding during an operation, such as reoperation or dissections known to be difficult. The first step in mitigating blood loss during an operation is prevention. Controlling haemorrhage and mitigating its clinical effects by appropriate fluid resuscitation are important components of intraoperative care[3,4].

In the human body, a fast-reacting and efficient blood coagulation system is in place, which is activated in any case of injury disrupting the integrity of blood vessels. After primary haemostasis

by the adherence and aggregation of thrombocytes at the site of the injury, this physiological system produces fibrin in order to stop blood loss and to generate a matrix which supports healing. This fibrin adhesion system initiates the last phase of 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- which is proteolytically cleaved and converted into fibrin monomers by the thrombin. The fibrin monomers polymerize to form insoluble fibrin. Thrombin also activates factor XIII that catalyses the formation of covalent bonds between molecules of fibrin to form a cross-linked clot capable of resisting dissolution. The presence of Ca^{++} is required for most reactions that lead to the generation of active thrombin.

In case of injuries which are accessible, the exertion of mechanical pressure would contribute to limitation of blood loss and improvement of haemostasis.

The potential reasons to use a hemostat agent in surgery are to improve the effectiveness of surgery, reduce complications, shorten operating room time, and increase the feasibility of minimally invasive surgery. The appropriate use of fibrin sealants can improve blood conservation and reduce intraoperative bleeding in certain procedures.

Fibrin sealants have been increasingly used as a biodegradable tissue sealant to stop or control bleeding in many surgical settings such as microvascular surgery, parenchymal tissue injury and resections, cardiovascular surgery, thoracic surgery, gastrointestinal surgery, hepatic and splenic surgery, dental surgery, plastic surgery, urology surgery, etc. Practical applications of FS products in orthopedic surgery, interventional radiology and minimally invasive endoscopy are growing .In practice, fibrin sealants have been demonstrated to be efficacious in controlling slowly bleeding foci, diffuse oozing, bleeding from needle puncture sites, lymphatic leaks, serous fluid collections, and diffuse parenchymal organ hemorrhage.

Fibrin sealants have been used to provide hemostasis, fortify anastomoses, and promote tissue healing by reducing inflammation and scarring, and to treat and prevent fistulas[5,6,7,8,9].

The use of human plasma proteins as tissue sealants dates back to early last century. The concept of using plasma fibrinogen mixed with thrombin to form adhesive was reported approximately in the 1930s[10]. Commercial concentrates rich in clottable fibrinogen became available in Europe in the late 1970s. More recently commercial FS products were also licensed for use in the United States of America (USA).

Risk factors:

Surgery may occur in any patients. Many risk factors have been associated with surgery. Some are preoperative patient characteristics, others are related to the type and severity of the disease itself and a third group are related to the type and extent of the surgical procedure.

The preoperative general risk factors should also have to be taken into consideration. The critical preoperative conditions of the patient has an important role; for instance if the patient has history of hypertension, diabetes, chronic renal failure with and without dialysis, chronic pulmonary disease defined by the long-term use of bronchodilators or steroids, patients who have cardiovascular risk factor (particularly diabetics or smokers). Morbidly obese patients with a body mass index of 33 or over and patients with systolic arterial blood pressure exceeding 140 and diastolic pressure exceeding 90, and previous cardiac surgery and chronic cardiac insufficiency.

Other rare general conditions could be analysed before a surgery is planned because there could be risk factors like immunosuppression with long-term immunosuppressive therapy, neurological dysfunction with neurological disease severely affecting ambulation or day-to-day functioning,

active neoplasm with malignant tumors present at operation, or a patient who refuses blood products[11].

The main existing treatment options:

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledges, and/or electrocautery. Absorbable hemostatic agents such as bovine gelatine power and sponges, and hemostatics 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 hemostasis.

The versatility of fibrin sealant is due to its capacity to cause blood to clot, creating a sealing barrier as well as gluing tissues together [12] .

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Uncontrolled haemorrhage from injury continues to be major source of morbidity and mortality for the patients who suffer a surgery.

In this study by Suneetha, Ramani and Moonesinghe (2011)[13] it was reported that an estimated 234 million surgical cases occur worldwide each year. There are data suggesting that in developed nations, surgical mortality may be between 0.4% and 0.8% and complications may occur in between 3% and 17% of patients. All-cause mortality within 1 year after most types of surgery is higher than mortality in age- and sex-matched normal populations, reflected as increased standardized mortality ratio; this increase in mortality is more frequent in patients who are high resource consumers while in the hospital (and therefore likely to have had a complicated postoperative course).These data highlight per operative morbidity and mortality as a major public health issue.

As a result, identification of high-risk surgical patients, and development of strategies aimed at reducing perioperative morbidity and mortality, is a major challenge.

In this other study C.D. Owners and, K Stoessel, (2008)[14] they define surgical site infections (SSIs) as infections occurring up to 30 days after surgery (or up to one year after surgery in patients receiving implants) and affecting either the incision or deep tissue at the operation site. Despite improvements in prevention, SSIs remain a significant clinical problem as they are associated with substantial mortality and morbidity and impose severe demands on healthcare resources. The incidence of SSIs may be as high as 20%, depending on the surgical procedure, the surveillance criteria used, and the quality of data collection.

Important co-morbidities

There are specific co-morbid diseases found in the target population but it depends on other variables patients' that would be confounding factors as age and sex.

The most common co- morbidities associated with the target population are these 13 categories of diseases: organic heart disease (OHD); ischemic heart disease (IHD); primary arrhythmias and conduction problems; congestive heart failure (no known IHD or OHD); hypertension; cerebral vascular accident; peripheral vascular disease; diabetes mellitus; respiratory problems; malignancies (excluding basal cell carcinomas of the skin); hepatobiliary disease; renal disease; and gastro-intestinal disease.

In order to see which patient variables were confounding the effect of co- morbidity on the rate of serious in-hospital complications, several factors suggested by previously published studies were considered as potential confounders: sociodemographic (age, sex, living alone, marital status and education level[15].

Co- morbid conditions are associated with the risk of death from coronary artery bypass graft surgery. Even after adjustment including age, sex, previous cardiac surgery, priority of surgery for other patient and disease characteristics, co- morbid conditions (especially diabetes, vascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, and dialysis-dependent renal failure) are associated with significantly increased risk of death after coronary artery bypass graft surgery [16].

Concomitant medication(s) in the target population:

There are no typical medications frequently used with this medicinal product to treat occasional vascular surgery. Nevertheless, we can consider general anaesthesia as a potencial concomitant medication and it is essential for some surgical procedures. General anaesthesia has become more complex but has improved to become safer and more routine than ever before. However, adults over 65 years of age are more likely to suffer other conditions that may require other medication(s).

Part II: Module SII - Non-clinical part of the safety specification

Preclinical studies for Grifols' fibrin sealant (FS Grifols) were established considering, as main guidelines, the European Union Guideline 2001/83CE, the ICH topic S6 "Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (CPMP/ICH/302/95), the ICH M3(M) "Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (CPMP/ICH/286/95, modification), and the ICH S7A "Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals" (CPMP/ICH/539/00). The following guidelines were also taken into account: "Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products" (CPMP/BPWG/1089/00), "Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use" from FDA/CBER (May 1999).

VeraSeal® complies with the pharmacopoeia and USA CFR requirements which are relevant for fibrin sealant.

The preclinical program of VeraSeal® is focused on the safety and efficacy of the product.

- Safety: with the aim to eliminate any possible adverse effect associated with the purification process, the composition of the product, acute toxicity studies of the component fibrinogen were performed by the intravenous route on rats and mice, and complementary safety studies of both components of the fibrin sealant in pigs (in cardiac and vascular surgery, and in liver surgery), and on rabbits (in vascular surgery).

- Efficacy: with the aim of evaluating the effectiveness of the product as local hemostatic and tissue sealant in surgery, a number of studies were performed on animals, in cardiac and vascular surgery and in liver surgery on pigs, and in vascular surgery on rabbits.

Key safety findings from non-clinical studies and relevance to human usage:
Toxicity

The results obtained from the acute toxicity studies performed, along with the additional information evaluated support the product safety and efficacy, as confirmed by the results from the clinical study itself. VeraSeal® is composed of the human blood-derived products fibrinogen and thrombin. Both products are normal constituents of human plasma. These homologous proteins are highly purified and do not show any functional modification in relation to fibrinogen and thrombin present in human plasma. In addition, these products can be defined as pertaining to well-known families of biological products. The components of VeraSeal® have been biologically characterized including the European Pharmacopoeia's specifications for this product and additional tests [(Fibrin Sealant Kit, monograph 01/2005:0903)]. The components used during the fibrinogen and thrombin production processes are undetectable or within specifications in the final product, guaranteeing the products' safety with regard to these substances. Fibrinogen and thrombin do not contain tranexamic acid, which in accordance with the "Core SPS for Plasma Derived Fibrin Sealant/Haemostatic Products" (EMA/CHMP/BPWP/598816/2010) should be quoted; nor do they contain any toxic excipient.

Studies on **reproductive toxicity**, **development genotoxicity**, or **carcinogenicity** were not performed since both fibrinogen and thrombin are naturally expressed human proteins which are not modified during the production process of FS Grifols.

As indicated in the ICH S1A consensus guideline "The need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95)", carcinogenicity studies are only recommended where there is some reason for concern about the carcinogenic potential of a product. This is not the case with VeraSeal®, since both components are naturally expressed human proteins.

As defined in the "Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products" (CPMP/BPWG/1089/00), since the product does not contain animal-derived active principles, the possibilities of **immunogenic reactions** are very remote, so preclinical studies on immunogenicity were not deemed necessary.

The intravenous acute toxicity studies of fibrinogen component [redacted] do not show lethality and no toxicity signs are observed in none of the animals given the product being tested. It should be taken into account that fibrinogen, component of fibrin sealant, is a product intended for topical use that in these studies is administered by intravenous route [redacted]. No significant changes are detected in none of the treated animals as refers to respiratory, circulatory, and autonomic and central nervous systems, somatomotor activity and behavior over the 14-day study period. Only 2 male rats, out of the 48 animals (24 mice and 24 rats) treated with the component fibrinogen, showed macroscopic alterations as well as weight alterations of the organs extracted. The microscopic exam of which discards any possibility of relationship with the experimental study. Therefore, it can be concluded that the product did not cause macroscopic alterations or weight alterations of the organs extracted. There were no alterations of the weight increase rate observed, in any of the animals, associated with the administration of the product.

In the case of thrombin, toxicological studies cannot be carried out by intravascular administration of the product because it is a thrombogenic protein that cannot be directly administered by intravenous route, Thrombin is partially absorbed by the fibrin clot, Thrombin is an enzyme whose precursor (prothrombin) is a natural protein circulating in human plasma and the excess of thrombin, if any, is inactivated by the protease inhibitors present in the blood. The possible toxicity of topically administered thrombin was studied when testing the fibrin sealant safety in the vascular and cardiac surgery study on pigs and rabbits.

Safety pharmacology

The preclinical program of VeraSeal® was focused on the safety and efficacy as a local hemostatic/tissue sealant in surgery.

Animal studies were performed applying the product in:

- Drops using cannula application: in vascular and cardiac surgery applying it to sutures or anastomosis performed on pigs´ heart, arteries and veins, and in vascular surgery applying it to abdominal aorta anastomosis on rabbits.

- Spray application: in liver surgery applying it in hepatic resection on pigs.

- **Vascular and Cardiac Surgery on Pigs**

The following sutures or anastomosis were carried out on Minipigs [redacted]

In this study was studied the Pharmacological safety by controlling vital signs, the local tolerability of the product and the possible effects of the mechanism of action or application of the product.

Product application did not induce hemodynamic, acid-base balance, electrocardiogram and analytical modifications. The product does not produce stenosis in the sutures of arteries, veins and bypass with venous or synthetic grafts, and no decrease of flows or increase of resistance index was recorded, neither during surgery nor within five weeks.

This fact, together with the adherences not increasing significantly and, the reabsortion of the product occurring during the first weeks, indicates that the fibrin sealant application can be expected not to increase, in the long term, the sutures stenosis or obstructions.

[redacted]

VeraSeal® is efficacious in the suture hemostasis, reducing the number of stitches, the need for supplementary and compression stitches to complete the hemostasis and the suture time, statistically significant differences being found in vascular sutures. The reduction in the number of stitches is not associated with the presence of false aneurysms. The internal surface of venous,

arterial and right atrium vessels is completely endothelium-covered and in no case did a false aneurysm occur.

No pulmonary leaks occurred after pulmonary resection and VeraSeal® application either. None of the animals developed a postoperative pneumothorax.

- **Vascular Surgery on Rabbits**

An anastomosis termino-terminal of the abdominal aorta with 4 equidistant points of polypropylene 8/0 was performed on 27 New Zealand rabbits. According to the application or not of FS, rabbits were distributed in three groups: A= control; B1= FS application after declamping the abdominal aorta; B2= FS application before declamping. The main group of the study is B2, which is the way the FS is normally applied.

The main objective of this study was to control the bleeding [redacted]

In terms of safety, and in the same way that the study on pigs, FS application does not induce any modification of the vital signs. The product does not produce stenosis, and does not exert any unfavorable action immediate and after 14 days in the quality of the anastomosis.

VeraSeal® is efficacious in suture hemostasis, reducing the bleeding of the anastomosis after the declamping and the duration of the surgery, without any decease of bleeding (equivalent to death) in the groups where the FS was applied (before or after), in contrast with the two deceases in the control group.

- **Liver Surgery on Pigs**

FS Grifols was used in liver surgery on 15 pigs. Spray application of the product without primary hemostasia in hepatic resection was performed.

The main objective of this study was to assess the FS Grifols safety, efficacy and applicability in spray. The animals were maintained during four weeks after surgery. After this period, they underwent new surgery in order to check the liver resection evolution.

FS Grifols is safe in spray application, did not induce modifications in vital signs during surgery nor were there complications after surgery. After 4 weeks the presence of inflammatory formation with eosinophils was detected in FS application area and into liver tissue. These minimal histopathology changes were due to foreign object reaction. This would be associated with the application of a human-derived product to pigs, and with the great amount of product applied.

The effectiveness of FS Grifols in liver surgery has been proved in this study on pigs. Spray application of the product without primary hemostasis in hepatic resection is possible and effective in order to achieve a complete hemostasis.

- **Hemostatic efficacy study for VeraSeal™ Dual Applicator:**

The objective of this study [redacted] was to evaluate and compare the hemostatic efficacy of FS Grifols when delivered by the VeraSeal™ Dual Applicator (referred to in the study as VistaSeal™ Airless Spray Accessory (ASA), Spray and Drip Mode, Open) and when delivered by the control device system. Comparison of hemostatic efficacy at designated time points were carried out using an acute swine liver resection model.

[redacted]

Two tests devices and two control devices were evaluated in the study:

	Open Spray device		Open Drip device	
	T1 (Test-1): FS Grifols + VeraSeal™ Dual Applicator Spray Tip (Open)	C1 (Control-1): FS Grifols + FibriJet® Gas-Assisted Spray Tip (Open)	T2 (Test-2): FS Grifols + VeraSeal™ Dual Applicator Drip Tip (Open)	C2 (Control-2: FS Grifols + FibriJet® Drip Tip (Open)
Success rate of hemostasis at 4 minutes	80% (16/20)	65% (13/20)	95% (19/20)	85% (17/20)
Success rate of hemostasis at 6 minutes	95% (19/20)	75% (15/20)	95% (19/20)	90% (18/20)

A one-sided 90% Confidence Interval (CI) was used to calculate for the proportion of success rate in each of test and control group. The result showed that both test articles had higher observed success rates on hemostatic efficacy than its control articles at both 4 minutes and 6 minutes.

In conclusion, the hemostatic efficacy of FS Grifols when delivered by VeraSeal™ Dual Applicator spray or drip tip (open) was comparable to that when delivered by the control device [redacted] in the swine liver resection model. The efficacy of FS Grifols is not impacted by the VeraSeal™ Dual Applicator or mode of delivery (spray or drip).

Other toxicity-related information or data

No special studies were deemed necessary. There has been no identified need for additional non-clinical data.

Part II: Module SIII - Clinical trial exposure

To date, VeraSeal® was evaluated in three phase 3 safety and efficacy clinical trials, completed at the time of this report. Subjects have been treated with FS Grifols as an adjunct to hemostasis during several surgical types such as vascular surgery (Study, IG1101), parenchymous tissue surgeries (Study IG1102), and soft tissue surgeries (Study IG1103).

A pediatric randomized, active controlled, single-blind, clinical trial (study IG1405) was conducted to evaluate the safety and efficacy of VeraSeal as an adjunct to hemostasis during open parenchyma (hepatic) surgery or soft tissue surgery.

The study of subjects undergoing peripheral vascular surgery is based on the design of previous studies with other FS products and past data [5-17-18], and on guideline documents published by the Food and Drug Administration (FDA) in May 1999 [19] and the European Agency for the Evaluation of Medicinal Products (EMEA) adopted in July 2004 [20], for the purposes of providing guidance for the submission of marketing authorization applications for this class of products.

The intended benefit of VeraSeal®' application is to support local hemostasis, particularly in situations where hemostatic measures based on conventional surgical techniques, such as suture, ligature or cautery, are ineffective or impractical

Clinical Trial Exposure:

The following studies will be explained in the RMP for safety evaluation:

a) Vascular Surgery: Study IG1101

The study IG1101 is intended to demonstrate that FS Grifols' application provides a measurable benefit when compared to hemostasis achieved through conventional surgical technique (suture) and by standard hemostatic action, such as mechanical pressure through manual compression (MC) entitled "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Peripheral Vascular Surgery". This is a multicenter clinical trial being carried-out in the United States of America (US), Hungary, Serbia and Russia.
This clinical trial consists of two parts: a Preliminary Part (I) and a Primary Part (II). All subjects enrolled in the Preliminary Part (I) will be treated with FS Grifols. Subjects in the Primary Part (II) will be randomized with 2:1 ratio into one of two treatment groups: FS Grifols or manual compression (MC).

In this study, where FS Grifols is topically administered by dripping, cumulative exposure is as follows: a total of 225 subjects underwent vascular surgery in the Preliminary (I) or Primary (II) part of the study (ITT Population). Of these, 59 were treated with FS Grifols in the Preliminary Part (I) of the study, 109 were randomized to receive FS Grifols in the Primary Part (II) of the study and 57 were randomized to manual compression (MC) treatment in the Primary Part (II) of the study.

FS Grifols was shown to be superior to the control group (manual compression) in achieving hemostasis by 4 minutes. Superiority was also established at the secondary efficacy endpoints by 5, 7, and 10 minutes.

Table 1: Duration of exposure (by indication)		
Vascular surgery		
Duration of exposure (at least)	Persons	Person time year*
Single topical administration (intra-operative)	168	Not applicable
Total person time	168	Not applicable

*Person time is not applicable as this study included a single dose

Table 2: By dose (by indication)		
Vascular surgery		
Mean dose of exposure	Persons	Person time*
4.23 mL in a topical administration	168	NA
Total	168	NA

The mean amount of FS Grifols used at the Target Bleeding Site was 4.23 mL among subjects in the safety population treated with FS Grifols (pooled).

*Person time is not applicable as this study included a single dose

Table 3: By age group and gender (by indication)				
Vascular surgery				
Age group	Persons		Person time*	
	M	F	M	F
Age group >3 year 11 years	0	0	NA	NA
Age group 12 years to 17 years	0	0	NA	NA
Age group 18 years to 65 years	70	29	NA	NA
Age group 66 years to 85 years	47	22	NA	NA
Age group >85 years	0	0	NA	NA
Total	117	51	NA	NA

*Person time is not applicable as this study included a single dose

Table 4: By ethnic or racial origin (by indication)		
Vascular surgery		
Ethnic/racial origin	Persons	Person time*
Ethnic origin White/Caucasian	145	NA
Black or African American	19	NA
Ethnic origin Asian	[redacted]	NA
Other	[redacted]	
Total	168	NA

*Person time is not applicable as this study included a single dose

As of final study report, 168 subjects have been treated with FS Grifols and evaluated for safety and a total of 427 AEs were reported. Twenty-one subjects (12.5%, 21/168) experienced 39 AEs (9.1%, 39/427) that were reported as potentially related to the IMP, classified as unlikely, possibly or probably (ADR).

Among all subjects, the most frequently reported AE preferred terms, more than 5% of the subjects, were procedural pain (58 [34.5%] and 21 [36.8%] subjects in the FS Grifols pooled and MC groups, respectively), pyrexia (19 [11.3%] and 6 [10.5%] subjects, peripheral edema (13 [7.7%]) in the FS Grifols compared with MC subjects (1 [1.8%]) and body temperature increased anemia and nausea 10 (6.0) in the FS Grifols.

The most common potentially related AEs, defined as an ADR, were procedural pain (4 [2.4%]) subjects) and nausea, pyrexia, vascular graft complication, parvovirus B19 test positive, and urinary retention (2 [1.2%] FS Grifols subjects each) were reported by more than 1 subject within a treatment group.

Serious Adverse Events (SAEs) were reported in thirty-four (20.2%) subjects in the FS Grifols group (pooled safety population) and experienced 60 SAEs, and 11 (19.3%) subjects in the MC group and experienced 14 SAEs.

From these SAEs only four subjects in the FS Grifols pooled group (2.4%) and one (1.8%) subjects in the MC group experienced SAEs that were considered potentially related to study treatment: postoperative wound infection and wound infection were considered unlikely related to study treatment, cellulitis and parvovirus B19 test positive were considered possibly related to study treatment.

AEs with outcome of death were more frequently reported among FS Grifols pooled subjects (4 subjects [2.4%]) than MC subjects (0 subjects). All were considered unrelated to the study treatment.

The purpose of this clinical trial was to obtain data to support licensure of a new human plasma derived FS (FS Grifols), manufactured by Instituto Grifols, S.A., Barcelona, Spain, by demonstrating that FS Grifols is both safe and effective in achieving hemostasis during vascular surgery.

b) Liver surgery: Study IG1102,

This study IG1102 is aim to evaluate the safety and efficacy of FS Grifols in subjects undergoing open surgical procedures where bleeding was present on parenchymous tissue was examined compared with Surgicel®, entitled "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Parenchymous Tissue Open Surgeries". This is a multicenter clinical trial being carried-out in the US, Hungary, Russia and Serbia.
In this study, where FS Grifols is topically administered by spraying, cumulative exposure is as follows a total of a total of 325 subjects were randomized into either FS Grifols group or Surgicel group (ITT Population). Among the subjects who were randomized in Part I + Part II of the study, 163 of 325 subjects were randomized to FS Grifols (ITT Population). Among the subjects who were randomized in Part I + Part II of the study, 162 subjects were randomized to Surgicel (ITT Population).

Table 1: Duration of exposure (by indication)		
Parenchymous Tissue Open Surgeries		
Duration of exposure (at least)	Persons	Person time year*
Single topical administration (intra-operative)	163	Not applicable
Total person time	163	Not applicable

*Person time is not applicable as this study included a single dose

Table 2: By dose (by indication)		
Parenchymous Tissue Open Surgeries		
Dose of exposure	Persons	Person time*
8.29 mL in topical administration	163	NA
Total	163	NA

The mean amount of FS Grifols used at the Target Bleeding Site was 8.29 mL among subjects in the safety population treated with FS Grifols (pooled),

*Person time is not applicable as this study included a single dose

Table 3: By age group and gender (by indication)				
Parenchymous Tissue Open Surgeries				
Age group	Persons		Person time*	
	M	F	M	F
Age group <2 year 11 years	[redacted]	[redacted]	NA	NA
Age group 12 years to 17 years	0	0	NA	NA
Age group 18 years to 65 years	51	55	NA	NA
Age group 66 years to 85 years	33	22		
Age group >85 years	[redacted]	[redacted]	NA	NA
Total	85	78	NA	NA

*Person time is not applicable as this study included a single dose

Table 4: By ethnic or racial origin (by indication)		
Parenchymous Tissue Open Surgeries		
Ethnic/racial origin	Persons	Person time*
Ethnic origin White/Caucasian	150	NA
Black or African American	[redacted]	NA
Ethnic origin Asian	10	NA
Other	[redacted]	
Total	163	NA

*Person time is not applicable as this study included a single dose

FS Grifols was shown to be non-inferior and additionally superior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes

As of final study report, 163 subjects have been treated with FS Grifols and evaluated for safety and a total of 737 AEs were reported. Eleven subjects (6.7%, 11/163) experienced 24 AEs (2.7%, 24/737) that were reported as potentially related to the IMP, classified as unlikely, possibly or probably (ADR).

Among all subjects, the most frequently reported AE preferred terms, more than 5% of the subjects, were procedural pain (59 [36.2%] and 61 [37.7%] subjects in the FS Grifols pooled and Surgicel groups, respectively), Nausea (34 [20.9%] and 38 [23.5%] subjects, hypotension (23 [14.1%]) in the FS Grifols compared with Surgicel subjects (10 [6.2%]) and anemia 22 (13.5) in the FS Grifols compared with Surgicel subjects (26 [16.0%]).

The most common potentially related AEs, defined as an ADR, were procedural pain, post procedural bile leak, pulmonary embolism and deep venous thrombosis (2 [1.2%]) FS Grifols subjects each) were reported by more than 1 subject within a treatment group.

Serious Adverse Events (SAEs) were reported in thirty (18.4%) subjects in the FS Grifols group (pooled safety population) and experienced 78 SAEs, and 23 (13.6%) subjects in the MC group and experienced 38 SAEs.

From these SAEs four subjects in the FS Grifols pooled group (2.4%) experienced 9 SAEs that were considered unlikely related to study treatment: three deep vein thromboses, two pulmonary embolisms, two post-procedural bile leaks, an abdominal abscess and a liver abscess.

AEs with outcome of death were more frequently reported among FS Grifols pooled subjects (7 subjects and 1 Surgicel subjects). All were considered unrelated to the study treatment.

c) Soft tissue surgery IG1103

The study IG1103 aims to evaluate the efficacy of FS Grifols as adjunct to hemostasis in soft tissue bleeding during retroperitoneal and pelvic surgical procedures, and during mastopexies and abdominoplasties. entitled "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Soft Tissue Open Surgeries". This is a multicenter clinical trial being carried-out in the US, Hungary and Serbia and FS Grifols is topically administered by dripping or spraying. Surgicel, a commercially available and widely used adjunct to hemostasis agent, was selected as the control.

This clinical trial consists of 2 parts: a Preliminary Part (I) and a Primary Part (II). Subjects in the Preliminary Part (I) of the study were to be randomized in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. Subjects in the Primary Part (II) of the study were to be randomized in a 1:1 ratio into FS Grifols or Surgicel treatment groups.

FS Grifols was shown to be non-inferior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes.

Overall, it was estimated that 736 subjects could have participated in both the Preliminary Part (I) and the Primary Part (II) of the clinical study. Pediatric subjects could have enrolled in both parts of the clinical study.

A total of 327 subjects were randomized into the study. In the Preliminary Part (I) of the study, 103 subjects were randomized. Of the 103 subjects, 51 subjects were randomized to the FS Grifols treatment group and 52 subjects were randomized to the Surgicel treatment group. In the Primary Part (II) of the study, 224 subjects were randomized. Of the 224 subjects, 116 subjects were randomized to the FS Grifols treatment group and 108 subjects were randomized to Surgicel.

Table 1: Duration of exposure (by indication)		
Soft Tissue Open Surgeries		
Duration of exposure (at least)	Persons	Person time year*
Single topical administration (intra-operative) **	169	Not applicable
Total person time	167+2	Not applicable

*Person time is not applicable as this study included a single dose

** Two (2) patients who were randomized to Surgicel® treatment received FS and have been categorized under FS for safety analyses. Therefore the total of patient exposed to FS is 169 (regardless of study part or randomization).

Table 2: By dose (by indication)		
Soft Tissue Open Surgeries		
Dose of exposure	Persons	Person time*
7.87 mL mean exposure in topical administration	169	NA
Total	169	NA

The mean amount of FS Grifols used at the Target Bleeding Site was 7.87 mL among subjects in the safety population treated with FS Grifols (pooled),

*Person time is not applicable as this study included a single dose

Table 3: By age group and gender (by indication)				
Soft Tissue Open Surgeries				
Age group	Persons		Person time*	
	M	F	M	F
Age group <2 year 11 years	7	[redacted]	NA	NA
Age group 12 years to 17 years	[redacted]	[redacted]	NA	NA
Age group 18 years to 65 years	23	104	NA	NA
Age group 66 years to 85 years	21	9		
Age group >85 years	[redacted]		NA	NA
Total	53	114	NA	NA

*Person time is not applicable as this study included a single dose

Table 4: By ethnic or racial origin (by indication)		
Soft Tissue Open Surgeries		
Ethnic/racial origin	Persons	Person time*
Ethnic origin White/Caucasian	139	NA
Black or African American	27	NA
Ethnic origin Asian	[redacted]	NA
Other	[redacted]	
Total	16 7 +2	NA

*Person time is not applicable as this study included a single dose

As of final study report, 169 subjects have been treated with FS Grifols and evaluated for safety and a total of 597 AEs were reported. Thirty-two subjects (32/169) experienced 65 AEs (65/597) that were reported as potentially related to the IMP, classified as unlikely, possibly or probably (ADR). ADRs were reported for 18.9% of FS Grifols subjects and 15.2% of Surgicel subjects. The most common ADRs were anemia, pyrexia, nausea, procedural pain, and pruritus

Among all subjects, the most frequently reported AE preferred terms were procedural pain (92 [54.5%] and 86 [54.4%], procedural nausea (24 [14.2%] and 31 [19.6%] and nausea (23 [13.6%] and 18 [11.4%] subjects in the FS Grifols pooled and Surgicel® groups, respectively). OR

The majority of ADRs were for single subjects. Exceptions were: procedural pain, nausea and pruritus (4 [2.4%]) subjects), anemia, insomnia, hypertension, leukocytosis, ileus, prothrombin time prolonged, ALT increased, AST increased, hypocalcemia, hypokalemia, hyponatremia, and headache (2 [1.2%] subjects each).

Serious Adverse Events (SAEs) were reported in seventeen (10.1%) subjects in the FS Grifols group (pooled safety population) and experienced 29 SAEs, and 18 (11.4%) subjects in Surgicel® group and experienced 27 SAEs. The most commonly reported SAEs were in the system organ class categories of infections and infestations and procedural complications

From these SAEs only one subjects in the FS Grifols pooled group (0.6%) and none subjects in Surgicel® group experienced two (2) SAEs (abdominal wound dehiscence and peritonitis) were considered possibly related to the study treatment and also attributable to application technique.

AEs with outcome of death were 3 that occurred during the study. All of the deaths started several days to weeks after surgery and were considered not related to study treatment.

In general, events reported in each clinical trial may be expected, in their nature, in populations suffering from severe diseases undergoing invasive surgical procedures.

d) Paediatric population: IG1405

As agreed with both FDA (IND 14986) and EMA, an exclusively-paediatric study (IG1405) was conducted as part of the Paediatric Investigational Plan of FS Grifols. The study was performed on paediatric subjects (<18 years old) undergoing an elective (non-emergency), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure, for the assessment of safety and efficacy of FS Grifols compared to EVICEL®. Emergency surgery was included in the last phases of the study to increase the chance for enrolling subjects in the newborn age subgroup (preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days)), by allowing enrollment of subjects undergoing emergency (non-elective) surgeries in this specific age subgroup only. EVICEL (Omrix Biopharmaceuticals NV, Diegem, Belgium) is a sterile solution manufactured from pooled human plasma, consisting mainly of a concentrate of human fibrinogen (55-85 mg/mL) and 1 vial of thrombin (800-1200 IU/mL).

A total of 178 children (< 18 years of age) were randomized and treated with VeraSeal (n=91) or active control (n=87). Of the 91 subjects treated with VeraSeal, 4 were ⩽ 27 days; 19 were ⩾ 28 days to ⩽ 23 months; 32 were ⩾ 2years to ⩽ 11 years; 36 were ⩾ 12 years to ⩽ 17 years. Forty-six children treated with VeraSeal underwent parenchyma (hepatic) surgical procedures and 45 had soft tissue surgeries. VeraSeal was shown to be non-inferior to the control group (EVICEL [sealant]) in achieving hemostasis by 4 minutes. The rate of hemostasis at the target bleeding site by 4 minutes was 96.7% (88/91 subjects) in the VeraSeal treatment group and was 95.4% (83/87) in the control group.

Enrollment and treatment has been completed (last patient last visit was achieved on 20-May-2022) and Clinical Study Report is currently under preparation.

Number of subjects exposed to FS Grifols and Evicel® for clinical trial IG1405*

Dummy Treatment	**Estimated number of subjects**
Drug (FS Grifols)	91
Comparator (Evicel®)	87
*Data are obtained after the IG1405 database lock as of 30 November 2022	

Number of subjects exposed to FS Grifols and Evicel® from clinical trial IG1405 by Age Group and Sex*

Age range **Estimated number of subjects**						
FS Grifols				Evicel®		
	Male	Female	Total	Male	Female	Total
Preterm and newborn infants (0 to 27 days)	0	4	4	0	2	2
Infants and toddlers (28 days to 23 months)	10	9	19	16	2	18
Children (2 to 11 years)	23	19	34	17	14	31
Adolescents (12 to 17 years)	19	17	38	27	9	38
*Data are obtained after the IG1405 database lock as of 30 November 2022						

Number of subjects exposed to FS Grifols and Evicel® from clinical trial IG1405 by racial group*

Racial group **Estimated number of subjects**		
	FS Grifols	Evicel®
Asian	[redacted]	[redacted]
Black/African American	5	[redacted]
Caucasian	83	85
Multi-racial (no primary race)	[redacted]	[redacted]
Other	[redacted]	0
Total	**91**	**87**
*Data are obtained after the IG1405 database lock as of 30 November 2022		

Summary of the clinical trials exposure among the 3 completed trials and pediatric study

A total of 591 subjects were exposed to FS Grifols among the 4 trials, including 307 male subjects, 292 female subjects, 102 pediatric subjects (≤16 years of age), 489 adult subjects (>16 years of age), and 172 elderly subjects (≥65 years of age).

A total of 176 SAEs within different ICSRs were reported for Fibrin Sealant clinical trials. Of these, 9 subjects and 15 events were serious, potentially related and unexpected (SUSARs). No SUSARs were reported in the pediatric study.

As these cases do not alter the safety profile of the product, the benefit-risk ratio of the product is not compromised.

Ongoing clinical trials

As of the DLP of this document, there are no ongoing clinical trials for Fibrin Sealant Grifols.

Part II: Module SIV - Populations not studied in clinical trials

To date, VeraSeal® has been studied in four clinical studies IG1101, IG1102,IG1103 and IG1405.

The study IG1101 is entitled "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Peripheral Vascular Surgery". In this study, where FS Grifols is topically administered by dripping, cumulative exposure is as follows a total of 225 subjects underwent vascular surger*y.* 168 subjects have been treated with FS Grifols and evaluated for safety.

This study IG1102 entitled "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Parenchymous Tissue Open Surgeries". In this study, where FS Grifols is topically administered by spraying, cumulative exposure is as follows a total of a total of 325 subjects. 163 subjects have been treated with FS Grifols and evaluated for safety.

The study IG1103 entitled "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Soft Tissue Open Surgeries". In this study, where FS Grifols is topically administered by spraying and by dripping, cumulative exposure is as follows a total of a total of 327 subjects. 169 subjects have been treated with FS Grifols and evaluated for safety.

Based on the number of patients exposed, the duration of patient exposure, total dose of medicine, action of medicine, we have detected one important potential risk of thromboembolic event.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programmes

Exclusion criteria may vary from study to study and, therefore, it is not possible to evaluate the effect of each of the exclusion criteria in the clinical trials. However, the effect of VeraSeal® was not studied in some populations.

Pregnant or lactating women

Reason for exclusion: Condition that could cause complications in the clinical trial setting. VeraSeal® is a normal constituent of the human plasma and acts as the endogenous molecule. The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. There is no data from clinical trials to know whether VeraSeal® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. VeraSeal® should be given to a pregnant woman only if clearly needed. Studies to evaluate the potential reproductive/development toxicity of VeraSeal® have not been performed.

Is it considered to be included as missing information? No

Rationale: Pregnancy and lactation have not been studied in clinical trials. The safety of VeraSeal® for use in pregnant women or breastfeeding has not been established in the studies. No safety concerns are expected in this population. No sufficient clinical and post-marketing data is available to consider VeraSeal® contraindicated for this population.

Paediatrics (<17 years of age)

Reason for exclusion: Surgery on children requires considerations which are not common in adult surgery. Children and adolescents are still developing physically and mentally making it difficult for them to make informed decisions and give consent for surgical treatments.

Is it considered to be included as missing information? No

Rationale: A total of 91 subjects treated with VeraSeal in IG1405 study, 4 were ≤ 27 days; 19 were ≥ 28 days to ≤ 23 months; 32 were ≥ 2years to ≤ 11 years; 36 were ≥ 12 years to ≤ 17 years in a pediatric randomized, active controlled, single-blind, clinical trial to evaluate the safety and efficacy of VeraSeal as an adjunct to hemostasis during open parenchyma (hepatic) surgery or soft tissue surgery. Additionally, IG1102 and IG1103 studies, mainly in adult subjects, eleven (11) paediatric subjects aged 16 years or younger were treated with VeraSeal.

Elderly (>89 years of age)

Reason for exclusion: Condition that could cause complications in the clinical trial setting.

Is it considered to be included as missing information? No

Rationale: The safety and effectiveness of VeraSeal® in adults older than 89 years old have not been established. Clinical trials with VeraSeal® had only a limited number of subjects (1 subjects) over the age of 85 have been enrolled and therefore, the information available on them is limited but with no special additional safety concerns.

Anaphylaxis or severe systemic response to any plasma-derived substance or other blood product(s)

Reason for exclusion: Individuals with known hypersensitivity against fibrinogen, thrombin or to any of the product excipients must not be treated with the product.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity reactions, including life-threatening anaphylactic reactions can occur even when a previous administration has been tolerated (including a negative test). Caution is therefore needed with every dose, even if previous tests have been made. No cases involving allergic/hypersensitivity reactions have been received up to the DLP of this document.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse drug reactions (ADRs) rare adverse reactions (frequency <1/10,000), adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

In general terms it can be said that the small sample size available observed in the post-marketing may difficult the detection of well-known adverse drug reactions to the product (active ingredient) setting such as true hypersensitivity or allergic reactions with low frequency occurrences.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Analysis of clinical studies for VeraSeal® showed that some populations were not studied in pre-authorization phase but this did not have implications regarding safety in the marketplace. Populations not studied included children, pregnant or nursing women, infection in the anatomic surgical area, elderly and patients with hypersensitivity to any of the product components.

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. There is no data from clinical trials to know whether can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. VeraSeal® should be given to a pregnant woman only if clearly needed. Studies to evaluate the potential reproductive/development toxicity of VeraSeal® have not been performed.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	The majority of the patients were white/Caucasian. Therefore, there are no data available in other different racial or ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

Elderly	No clinical trial experience with geriatric population is available. Clinical trials with VeraSeal® had only a limited number of subjects over the age of 85 enrolled and therefore, the information available on them is limited but with no special additional safety concerns.
Children	Surgery on children requires considerations which are not common in adult surgery. Children and adolescents are still developing physically and mentally making it difficult for them to make informed decisions and give consent for surgical treatments. The safety and efficacy of VeraSeal® in children aged ≤17 years have not been established in the clinical trials, only have been included small number of paediatric population in the studies IG1103 and IG1102. A total of 91 subjects treated with VeraSeal, 4 were ≤ 27 days; 19 were ≥ 28 days to ≤ 23 months; 32 were ≥ 2years to ≤ 11 years; 36 were ≥ 12 years to ≤ 17 years in a pediatric randomized, active controlled, single-blind, clinical trial to evaluate the safety and efficacy of VeraSeal as an adjunct to hemostasis during open parenchyma (hepatic) surgery or soft tissue surgery.

Part II: Module SV - Post-authorisation experience

FS Grifols has been approved eleven (11) countries: Australia, Canada, Europe, United Kingdom, United States, Switzerland, Singapore, Taiwan, India, South Korea and Brazil.

SV.1 Post-authorisation exposure

The total number of vials and syringes, regardless of their size, has been considered as a good marker of the number of doses received by the patients that have been exposed to individualized application of the FS. Therefore, it is assumed that one vial is equivalent to a patient. Individual doses typically ranged from 0.3 to 18.0 mL in the clinical studies. Dose depends on variables including, but not limited to, the type of surgical intervention, the size of the area, the intended application method, and the number of applications.

It is not possible to accurately estimate the amount of product that has been distributed according to sex, race or age. Similarly, it is not possible to precisely estimate the frequency of use of the product in special populations such as the elderly, children, pregnant or lactating women, patients with renal or hepatic impairment, patients with other co-morbidities, patients with disease severity different from that studied in clinical trials, sub-populations carrying relevant genetic polymorphisms or populations with specific racial and ethnic origins.

The total amount of Fibrin Sealant distributed by the manufacturer from first sales data available (01-Aug-2019) to data lock point (30-Nov-2022) was 859,827 vials, corresponding to 859,827 estimated number of estimated doses.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

VeraSeal® is not known to be associated with any potential for misuse for illegal purposes. No evidence of an illegal use has been found in the literature reviewed.

This product will be dispensed in the hospital pharmacy to use only in surgery patients.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The classification of the identified and potential risks was based on the well-known safety profile of Fibrinogen (Human) and Thrombin (Human) in general (class labeling) and a comprehensive review of the safety profile of VeraSeal®.

There are no important identified, potential risks, and missing information for VeraSeal®.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as it is not an initial RMP. It is the first time that this RMP has been issued in order to adapt the document to the new format.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as it is not an initial RMP. It is the first time that this RMP has been issued in order to adapt the document to the new format; therefore, no new safety concerns have been included in the list of safety concerns.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The important risks and missing information detailed below have been removed from the Summary of the safety concerns in line with criteria set in revised GVP V concerning removals of important risks and missing information items. All Parts, Sections and Tables of the RMP have been updated to reflect the further changes to the Summary of the Safety concerns.

- Hypersensitivity/allergic reactions, including severe anaphylaxis
- Antibodies against components of fibrin sealant
- Transmission of infectious agents
- Thromboembolic events
- Tissue adhesion
- Medication error
- Use in women who are pregnant or lactating
- Use in tissue gluing
- Use in neurosurgery
- Use in application through a flexible endoscope
- Use for gastrointestinal anastomoses

Due to Assessment Report for Procedure no.: EMEA/H/C/004446/II/0006/G, all the safety concerns have been removed from the Risk management plan, but should still remain safety concerns listed in the PSUR, as both documents have a different focus and different definitions for safety concerns. The safety concerns should therefore still be monitored and discussed in future PSURs.

SVII.3 Details of important identified risks, important potential risks, and missing information

The Summary of Data and Guidance for the Investigator states the information below listed in regards to warnings, precautions and interactions of the substance. Furthermore the SPC for the aforementioned product is in line with other fibrin sealant products authorised in the EMA.

Most of the information regarding contraindications or warnings and precautions is class-related, i.e., common for the fibrin sealant products. Thus, information can be found in general monographs, rather than derived from specific studies.

Due to this fact, the current product information is written in order to contain any class-related information, but bearing in mind that some side effects have never been described for VeraSeal® itself.
The product is used in populations described in clinical study and it has described below the identified/potential risks from clinical development.

SVII.3.1. Presentation of important identified risks and important potential risks

There are no important identified and potential risks for VeraSeal®. No safety concerns identified.

SVII.3.2. Presentation of the missing information

There is no missing information for VeraSeal®. No safety concerns identified.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None identified
Important potential risks	• None identified
Missing information	• None identified

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The present Pharmacovigilance Plan provides details of the pharmacovigilance activities to be applied to the medicinal products containing VeraSeal®, by reviewing each safety concern of the product as noted in Part II S VIII *Summary of the safety concerns* of the present RMP.

The pharmacovigilance (PV) system implemented at Grifols provides a mechanism to report, collect and assess suspected adverse event reports with Grifols products licensed worldwide. It allows assessment of adverse events for expedited and timely evaluation and provides information on the safety profile of the products. The PV system in place is useful to identify if reported cases are related to VeraSeal®.

Routine literature searches are also undertaken to identify reports of potential adverse events in which a Grifols product is reasonably considered suspect. If the brand of product is not identified in such a literature report, then it is conservatively assumed to be a Grifols product, and follow up is initiated to confirm the actual market authorization holder. Grifols PV Department up also monitors serious adverse events (SAEs) from company-sponsored clinical trials, and oversees any applicable regulatory reporting of these SAEs.

No special safety concerns were arisen in the clinical study performed with VeraSeal®. Routine pharmacovigilance activities have been considered sufficient for post-authorisation safety monitoring. These routine pharmacovigilance activities have not been included since they are specified in the Pharmacovigilance System Master File.

Instructions to properly use the product have been stated in the product leaflets.

III.2 Additional pharmacovigilance activities

There are currently no ongoing or planned additional pharmacovigilance activities for VeraSeal®.

III.3 Summary Table of additional Pharmacovigilance activities

This section is not applicable as there are no specific ongoing or planned additional PV activities in the Pharmacovigilance Plan.

Part IV: Plans for post-authorisation efficacy studies

Analysis of clinical safety showed that the use of VeraSeal® was well tolerated in the subject population; the vast majority of adverse events received were consistent with the described reactions known to occur with local haemostatics.

Overall the review of the safety data suggests that the product safety profile remains consistent with the approved labelling, and there is an overall favourable benefit-to-risk ratio.

There are no on-going or planned imposed post-authorisation efficacy studies (PAES) to be performed with VeraSeal® in the target population.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

As per all the data available coming from clinical trial experience (detailed in the previous sections), there are no special safety identified risks. The important identified and potential risks are those expected for this type of population, therefore a risk minimisation plan is not needed.

V.1. Routine Risk Minimisation Measures

The risk minimization activities suggested are the warnings included in the product information that comes from the product leaflets.

Table Part V.1: Description of routine risk minimisation measures by safety concern

This table is not applicable as there are no safety concerns for the product.

V.2. Additional Risk Minimisation Measures

There are no additional risk minimization measures for VeraSeal®.

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

This table is not applicable as there are no safety concerns for the product.

Summary of risk management plan for VeraSeal® (Fibrin Sealant Grifols)

This is a summary of the risk management plan (RMP) for VeraSeal®. The RMP details important risks of VeraSeal®, how these risks can be minimised, and how more information will be obtained about VeraSeal® risks and uncertainties (missing information).

VeraSeal® Package Information and its patient information give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for VeraSeal should be read in context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VeraSeal's RMP.

I. The medicine and what it is used for

VeraSeal® is indicated as a supportive treatment in adults and children where standard surgical techniques are insufficient: for improvement of haemostasis and as a suture support in vascular surgery.

It contains Fibrinogen (Human) and Thrombin (Human) as the active substances and it is given as a solution for sealant.

Further information about the evaluation of VeraSeal's benefits can be found in VeraSeal's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of VeraSeal®, together with measures to minimise such risks and the proposed studies for learning more about VeraSeal® risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information (such as warnings, precautions, and advice on correct use) in the Package Insert and Patient Information addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of VeraSeal® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of VeraSeal® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VeraSeal®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	• None identified
Important potential risks	• None identified
Missing information	• None identified

II.B Summary of important risks

There are no important identified, potential risks or missing information for VeraSeal®. No safety concerns identified.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of VeraSeal®.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for VeraSeal®.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

This section is not applicable as there are no specific adverse drug reaction follow-up forms.

Annex 6 - Details of proposed additional risk minimisation activities

This section is not applicable as there are no proposed additional risk minimisation activities.