Annex 1:
Relevant sections of the TachoSil sealant matrix "Summary of Product Characteristics" that have been revised (amendments to the text are indicated in **bold**)

Summary of Product Characteristics

4.4 Special warnings and precautions for use

For epilesional use only.

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

Specific data have not been obtained on the use of this product in neurosurgery or in gastrointestinal anastomoses surgery.

As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately.

To prevent the development of tissue adhesions at undesired sites, ensure tissue areas outside the desired application area are adequately cleansed before administration of TachoSil (see section 6.6). Events of adhesions to gastrointestinal tissues leading to gastrointestinal obstruction have been reported with use in abdominal surgery carried out in proximity to the bowel.

In case of shock, the current medical standards for shock treatment should be observed.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

It is strongly recommended that every time TachoSil is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product.

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.

Thromboembolic complications may occur if the preparation is unintentionally applied intravascularly (see section 4.4).

For viral safety see section 4.4

Frequency of undesirable effects for TachoSil based on all adverse event data from six clinical trials, two post-authorisation safety studies and spontaneous reporting.

Summary of the safety profile
The safety data of TachoSil generally reflect the type of post-operative complications related to the surgical settings in which the trials were conducted and the underlying disease of the patients.

Tabulated summary of adverse reactions
Data from the six controlled clinical trials conducted by the MAH has been pooled into an integrated dataset. The frequencies of occurrence in this SmPC originate from this integrated dataset. In the integrated analyses, 521 patients were treated with TachoSil and 511 patients were treated with comparator treatment. Due to practical reasons (comparison to standard surgical and standard haemostatic treatment), blinding was not possible in the TachoSil trials. Therefore the studies were performed as open-label studies.

The following categories are used to rank the undesirable effects by frequency of occurrence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); and very rare (<1/10,000), not known (cannot be estimated from the available data).

Frequency Organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	~~**Very rare (<1/10,000), not known (cannot be estimated from the available data)**~~**Frequency not known**
Immune system disorders		Hypersensitivity	
Vascular disorders			Thromboembolism (if applied intravascularly)
Gastrointestinal disorders			**Intestinal obstruction (in abdominal surgeries)**
General disorders and administration site conditions	Pyrexia*		**Adhesions**

*Pyrexia occurred in 6.3% of the patients treated with TachoSil and in 5.9% of the patients treated with comparator treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

6.6 Special precautions for disposal and other handling

TachoSil comes ready to use in sterile packages and must be handled accordingly. Use only undamaged packages. Once the package is opened, post-sterilisation is not possible. The outer aluminium foil sachet may be opened in a non-sterile operating area. The inner sterile blister must be opened in a sterile operating room area. TachoSil should be used immediately after opening the inner sterile cover.

TachoSil is used under sterile conditions. Prior to application the wound area should be cleansed, e.g. from blood, disinfectants and other fluids. After removal of the conventional, flat TachoSil from the sterile package it should be pre-moistened in saline solution and then applied immediately. The yellow, active side

of the matrix is applied to the bleeding/leaking surface and held against it with a gentle pressure for 3-5 minutes. This procedure enables an easy adhesion of TachoSil to the wound surface.

After removal of the pre-rolled TachoSil from the sterile package it should be applied immediately through the trocar **without** pre-moistening. While unrolling the matrix the yellow, active side of the matrix is applied to the bleeding/leaking surface using e.g. a pair of cleansed forceps and held against it with a moist pad under gentle pressure for 3-5 minutes. This procedure enables an easy adhesion of TachoSil to the wound surface.

Pressure is applied with moistened gloves or a moist pad. Due to the strong affinity of collagen to blood, TachoSil may also stick to surgical instruments**,** ~~**or**~~ gloves **or adjacent tissues** covered with blood. This can be avoided by cleansing surgical instruments**,** and gloves **and adjacent tissues** before application. **It is important to note that failure to adequately clean adjacent tissues may cause adhesions (see section 4.4).** After pressing TachoSil to the wound, the glove or the pad must be removed carefully. To avoid TachoSil from being pulled loose it may be held in place at one end, e.g. with a pair of forceps.

Alternatively, e.g. in case of stronger bleeding, TachoSil may be applied without pre-moistening, while also pressing gently to the wound for 3-5 minutes.

The active side of TachoSil should be applied so that it extends 1-2 cm beyond the margins of the wound. If more than one matrix is used they should overlap. TachoSil can be cut to the correct size and shaped if too large.

Pre-rolled TachoSil can be used for both open surgery and in minimally invasive surgery, and it can pass through a 10 mm or larger port or trocar.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

2. What you need to know before TachoSil is used

Warnings and precautions

TachoSil is for local use only and should not be applied inside a blood vessel. Blood clots may occur if TachoSil is unintentionally applied inside a blood vessel.

It is possible that you could suffer an allergic reaction after TachoSil has been applied. You may suffer hives, or a rash similar to nettle rash, chest discomfort or tightness, wheezing or low blood pressure. You should contact your doctor immediately if you discover any of these symptoms.

After abdominal surgery and if TachoSil sticks to nearby tissues, it is possible that scar tissues can develop in the operated area. Scar tissues can cause surfaces in your bowel to stick together, which can lead to blockage of the bowel.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to the patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant woman (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia, (e.g. sickle cell disease or haemolytic anaemia).

It is strongly recommended that when you receive TachoSil the name and batch number of the product are recorded at the hospital in order to maintain a record of the batches used.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

TachoSil is made on the basis of human blood. All medicines based on human blood may uncommonly cause allergic reactions. In isolated cases these allergic reactions may progress to anaphylactic shock. These allergic reactions may occur especially if TachoSil is used repeatedly or if you are allergic to any of the ingredients in TachoSil.

In rare cases you may produce antibodies against the active substances of TachoSil. You may experience a fever when taking TachoSil.

Scar tissues may develop in some patients after surgery and use of TachoSil. Bowel obstruction and pain following abdominal surgeries can also occur. The frequency of these types of events is not known (cannot be estimated from available data). Your surgeon will make sure to clean the operating area when applying TachoSil to reduce this risk.

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.