TISSEEL Ready to use

(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627

UKPAR

TABLE OF CONTENTS

Lay summary P2
Scientific discussion P3
Steps taken for assessment P46
Summary of product characteristics P48
Product information leaflet P61
Labelling P67
TISSEEL Ready to use

(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627

LAY SUMMARY

The MHRA granted Baxter Healthcare Ltd. a Marketing Authorisation (licence) for the medicinal product TISSEEL Ready to use (PL 00116/0627) on the 3rd of October 2008. This is a prescription only medicine (POM) and is indicated as a supportive treatment, when standard surgical techniques are insufficient, for:

- The improvement of hemostasis (stopping bleeding)
- As a tissue glue to promote adhesion/sealing, or as suture (stitches) support, in gastrointestinal anastomoses (joining together of intestines after surgery to remove part of it) and in neurosurgery (brain surgery) where contact with cerebro-spinal fluid or dura mater (the outer membrane covering the brain) may occur.

TISSEEL is a two-component tissue sealant, and it contains two of the proteins that make the blood clot. These proteins are called fibrinogen and thrombin. When these proteins mix during application, they form a clot where the surgeon applies them. During surgery, tissues may bleed and it may not be possible for the surgeon to control this bleeding by using stitches, or by applying pressure. TISSEEL is applied to the surface of tissues, either to control bleeding, or to stop (or prevent) leaks of other types of fluid, by creating a watertight seal.

The clinical data presented to the MHRA, pre licensing, demonstrated that TISSEEL Ready to use is clinically equivalent to the currently licensed product Tisseel Kit (VH), Two-Component Fibrin Sealant (PL 00116/0321). No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking TISSEEL Ready to use outweigh the risks; hence a Marketing Authorisation has been granted.
TISSEEL Ready to use
(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction                  P4
Pharmaceutical Assessment    P5
Pre-Clinical Assessment      P24
Clinical Assessment          P31
Overall conclusions and risk benefit assessment P45
INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to Baxter Healthcare Ltd. for the medicinal product TISSEEL Ready to use (PL 00116/0627) on the 3rd of October 2008. This product is a prescription only medicine.

The application for TISSEEL Ready to use was submitted as a national standard abridged application for a known active substance under Article 8.3 of Directive 2001/83/EC as amended. This application is a line extension to the currently licensed product Tisseel Kit (VH), Two-Component Fibrin Sealant (PL 00116/0321), and is an updated frozen version of the cross-referred product.

TISSEEL Ready to use is indicated as supportive treatment, where standard surgical techniques are insufficient, for:

- a) The improvement of hemostasis
- b) As a tissue glue to promote adhesion/sealing, or as suture support:
  - In gastrointestinal anastomoses
  - In neurosurgery where contact with cerebro-spinal fluid or dura mater may occur

TISSEEL Ready to use is a fibrin/tissue sealant. Fibrin sealants are composed of two essential ingredients: thrombin and fibrinogen, which both promote hemostasis. TISSEEL Ready to use mimics the final stage of the blood coagulation cascade using high concentrations of fibrinogen and thrombin.

TISSEEL Ready to use is a biological, double virus inactivated two-component fibrin sealant produced from pooled human plasma. Component 1 is the Sealer Protein Solution, containing Sealer Protein and Aprotinin, and Component 2 is the Thrombin Solution containing Thrombin and Calcium Chloride. Both components, Sealer Protein Solution and Thrombin Solution, are supplied deep-frozen and are ready to use upon thawing. The two components are combined immediately before the product is applied to the patient.
QUALITY ASSESSMENT

INTRODUCTION

Legal Basis
This line extension application is submitted in accordance with Directive 2001/83/EC as amended, Art 8.3. It is filed as a National Standard Abridged application.

Use: Local Hemostasis & Tissue Adhesives
This product is an updated frozen version of the currently licensed product Tisseel Kit (VH S/D), Two-Component Fibrin Sealant (PL 00116/0321). Both products are considered clinically equivalent.

Fibrin Sealant VH S/D Frozen is a biological, double virus inactivated two-component fibrin sealant produced from pooled human plasma. Component 1 is the Sealer Protein Solution, containing Sealer Protein and Aprotinin, and Component 2 is the Thrombin Solution containing Thrombin and Calcium Chloride. Both components, Sealer Protein Solution and Thrombin Solution, are supplied deep-frozen and are ready to use upon thawing. The two components are combined immediately before the product is applied to the patient.

Legal Status
Subject to Medical Prescription

DRUG SUBSTANCE: SEALER PROTEIN SOLUTION – FROZEN

General information
A monograph for the Fibrin sealant kit is included in the European Pharmacopoeia (Ph Eur 0903), and fibrinogen concentrate is one of its components. Fibrinogen is contained in human plasma. Upon injury, soluble fibrinogen is cleaved by thrombin, and forms an insoluble network of fibre bundles, the fibrin clot. This results in haemostasis and a matrix which supports the natural wound healing process. During the course of wound healing the fibrin clot is completely degraded and replaced by newly formed tissue.

The final stage of the blood coagulation process, i.e. the natural mechanism of clot formation, is imitated by fibrin sealant.

Nomenclature
INN: Human fibrin
ATC-code: B02BC local haemostatics
V03AK tissue adhesive

Structure
Satisfactory information on the structure of human fibrinogen has been provided from literature.

Manufacture

Manufacturers
The manufacturing sites involved in the production of sealer protein have been satisfactorily identified.
Description of Manufacturing Process and Process Controls
Satisfactory description of the manufacturing process and process controls is provided. The in-process controls applied are generally appropriate and appear to give a reproducible product.

Filling, Storage & Transport
Internal transports are performed according to written procedures.
At the minimum, the following information is recorded on the labels: Product name, Resource number, Lot number and Storage temperature.
A transfer protocol containing the following information is delivered along with the transport containers: Product name, Lot number, Amount / weight, Storage temperature, Originator and Recipient Departments, Date and signature.
The cryoprecipitate, portioned in labelled plastic buckets, which are closed and frozen, is transported from one manufacturing site to another manufacturing site. The portioned cyroprecipitate may be stored at \( \leq -20^\circ\text{C} \) for up to 12 months.
The vapour heated Sealer Protein Bulk is filled into double polyethylene bags, which are sealed and labelled and may be stored at \( \leq -20^\circ\text{C} \) for up to 12 months or at room temperature for up to 4 days.

Control of Materials
Human plasma, complying with the requirements of the Ph. Eur. Monograph on Human Plasma for Fractionation (0853), and with the Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95) is used as the starting material for the manufacture of Sealer Protein Bulk. In addition, the collected plasma used as source material is in compliance with all European and US regulations, certified centrally by the EMEA under the number EMEA/H/PMF/000003/2004 (updated annually most recently updated 24 April 2008).

The raw materials used in the manufacture of Sealer Protein Bulk and Drug Product comply with current compendial specifications. A supplier qualification program and regular audits have been established, and certificates of analysis have been provided. Incoming materials are tested for identity and additional tests as specified. Conductivity and bioburden of Water for injections is regularly monitored.

Controls of Critical Steps and Intermediates
The critical steps for the manufacture of Sealer Protein Bulk are those contributing to significant viral reduction. Deviations from the defined limits result in an investigation according to Baxter’s established exception management process. The system ensures that deviations are duly documented and appropriate actions are initiated.

Process Validation and/or Evaluation
Three consecutive conformance lots of Sealer Protein Bulk were produced according to the approved validation protocol with the established acceptance criteria. All validation activities were performed at the manufacturing scale. All specifications and in-process controls were met.

Manufacturing Process Development
The Sealer Protein VH S/D drug product has been developed in order to enhance viral safety without changing the content of clottable protein or affecting performance. In addition to the current method of vapour heat treatment, a second dedicated virus
inactivation step (S/D treatment) has been incorporated into the manufacture of the Sealer Protein Bulk of Fibrin Sealant VH S/D. The combined use of these independent viral inactivation methods further increases the viral safety margin of the product. In addition, the handling properties of the Sealer Protein Bulk and Sealer Protein VH S/D drug product have been improved. Critical manufacturing limits have been identified and the influence of deviations from these limits on product quality and yield has been examined.

**Characterisation**

**Elucidation of Structure and other Characteristics**
The active ingredient of the Sealer Protein Bulk is human plasma-derived fibrinogen. Fibrinogen has a molecular weight of approximately 340 kDa and is comprised of six polypeptide chains, i.e. two sets of three polypeptide chains termed alpha, beta, and gamma that are joined by disulfide bridging. The clot structures and protein composition of Fibrin Sealant VH S/D and the predecessor product TISSEEL VH were examined by scanning electron microscopy (SEM) and SDS-PAGE.

**Impurities**
Sealer Protein Bulk is a human plasma-derived material that contains a high amount of fibrinogen. Other proteins originating from human plasma are part of the preparation and have been identified as product-related substances. Materials introduced throughout the manufacturing process for different purposes and reduced to residual levels by the subsequent process steps have been identified and listed as process-related impurities.

**CONTROL OF DRUG SUBSTANCE: SEALER PROTEIN SOLUTION–FROZEN**

**Drug Substance Specification**
The drug substance specification has been provided and is compliant with the Ph. Eur. Monograph (Fibrin Sealant Kit: 0903).

**Analytical Procedures**
Details of the analytical procedures have been provided. They are compendial methods and are considered appropriate.

**Validation of Analytical Procedures**
Validation reports for the pharmacopoeial analytical methods are not presented. The methods used for the Determination of Protein Content and the Determination of Fibrinogen Content (Clottable Protein) are modified from methods described in Ph. Eur. (Fibrin Sealant Kit: 0903). For these tests, validation according to CPMP/ICH/381/95 and CPMP/ICH/281/95 was performed.

**Batch Analyses**
Results from the quality control testing of Sealer Protein Bulk production scale conformance lots have been provided. All results are well within the specifications and demonstrate the consistent manufacture of Sealer Protein bulk.
Justification of Specification
The specification is based on a combination of compendial limits, existing manufacturing and process development data, toxicity studies, historical experience with Baxter’s predecessor fibrin sealant products, process capabilities, analytical method validation data and product stability data.

Reference Standards or Materials
N/A

Container Closure System
This has been adequately described and specifications of the drug substance containers have been provided. Compatibility of the container closure system with the drug substance (Sealer Protein Bulk) has been demonstrated by stability studies, which have confirmed the suitability of the container closure system for the storage of Sealer Protein Bulk.

Stability

Stability Summary and Conclusions
The data provided generally support the physicochemical and biological stability of the drug substance under the storage and handling conditions described.

Stability Data
Stability studies have been conducted with three conformance lots of Sealer Protein Bulk used for production of the drug product, and included long-term testing of the intermediate Cryoprecipitate. Data up to 15 months did not show any significant changes during the whole period of observation, and therefore support the shelf life proposed and confirm the suitability of the container.

DRUG PRODUCT: SEALER PROTEIN SOLUTION – FROZEN

Composition of the Drug Product
Sealer Protein Solution is one of the components of Fibrin Sealant VH S/D Frozen. It is a sterile, non-pyrogenic, vapour-heated, solvent detergent-treated, frozen solution made from pooled human plasma and bovine aprotinin.

Sealer Protein Solution contains human plasma derived fibrinogen and aprotinin (Bovine) as active ingredients. Fibrinogen functions as a clot forming agent and aprotinin as a fibrinolysis inhibitor.

Sealer Protein Solution is filled into one chamber of the double-chamber plastic syringe, which is the final container of the product. (Thrombin Solution, the second component of Fibrin Sealant VH S/D Frozen, is filled into the other chamber of the double-chamber plastic syringe.)

Dosage Form Description
Fibrin Sealant VH S/D Frozen consists of a double-chamber syringe containing equal volumes of the Sealer Protein Solution and of the Thrombin Solution. Each solution is filled into one chamber of the syringe. The product is available in 2ml, 4ml and 10ml pack sizes, with the 2ml pack size containing 1ml Sealer Protein Solution and 1ml Thrombin Solution; the 4ml pack size containing 2ml of each solution, and the 10ml pack
size containing 5ml of each solution, respectively. Fibrin Sealant VH S/D Frozen is thawed prior to use and then applied using the application device (Duo Set) supplied with the product.

The Duo Set, which is a set of sterile accessory devices packed with the syringe, consists of the following components:

1. Joining Pieces (2 pcs, with tether strap)
2. Application needles (4 pcs, blunt)
3. Double Syringe Plunger (1 pc)

The Duo Set is designed to simultaneously apply identical amounts of Sealer Protein Solution and Thrombin Solution.

**Pharmaceutical Development**

The development pharmaceutics were satisfactorily presented and the issues addressed include the rationale for the formulation and its subsequent evolution, and the manufacturing process development. Development studies on packaging materials were provided. Chemical and physical compatibility were demonstrated in the course of the finished product stability studies.

**Manufacture**

**Batch Formula**

The Sealer Protein Solution Batch formula has been provided for an average batch size.

**Description of Manufacturing Process and Process Controls**

A satisfactory account of the manufacturing process has been provided. The in-process controls applied are appropriate and meet the required acceptance criteria. Appropriate control tests are applied to the final container samples for release testing, and until the completion of tests, the final containers are quarantined.

**Control of Critical Steps and Intermediates**

The critical steps have been described.

**Process Validation and/or Evaluation**

Three conformance lots of Sealer Protein Solution were manufactured to demonstrate process consistency. In-process parameters and controls have been monitored to evaluate the reliability of the process. The process was appropriately validated and is considered capable of producing a drug product of adequate quality, conforming to predetermined parameters and acceptance criteria. The only exception was the bioburden level before sterilising filtration for two lots. Investigation into the cause of the increased bioburden levels was performed and preventive actions were therefore implemented. Four lots that have been subsequently produced using the same equipment confirmed the adequacy of investigation and demonstrated the effectiveness of the corrective actions.

Samples taken from the bottom and the top layers of the vessel were analysed for protein content. All lots complied with the acceptance criteria demonstrating the homogeneity of the bulk solution after volume adjustment.

Sterile Filling, Packaging and Freezing were satisfactorily validated. The validation results demonstrated that the in-process parameters and controls are within the established limits. The Sealer Protein Solution was validated for lot homogeneity.
throughout filling, for holding time prior to freezing and for aseptic conditions during sterilising filtration.

Overall, the data demonstrate that the process is capable of producing bulk Sealer Protein Solution and filled containers which are homogeneous and of acceptable and consistent quality.

Control of Excipients

Specifications
All excipients used in the pharmaceutical production of Sealer Protein Solution, i.e. Human Albumin, Niacinamide, Aprotinin and Water for Injections, comply with the current edition of the Ph. Eur. Analytical procedures for the tests regarding the excipients are performed according to the requirements of the current Ph. Eur. monographs, and the specifications of the excipients are set to comply with the current edition of the Ph. Eur.

Control of Drug Product

Finished Product Specification for Sealer Protein Solution
The finished product specification has been provided and is compliant with the Ph. Eur. Monograph.

Analytical Procedures
Details of the analytical procedures have been provided. Most are compendial methods and are considered appropriate.

Validation of Analytical Procedures
Validation reports for the pharmacopoeial methods are not presented. The methods used for the Determination of Protein Content and the Determination of Fibrinogen Content (Clottable Protein) are modified from methods described in Ph. Eur. (Fibrin Sealant Kit: 0903). For these tests, validation according to CPMP/ICH/381/95 and CPMP/ICH/281/95 was performed.

Batch Analyses
Results from the quality control testing of Sealer Protein Solution production scale conformance lots were provided for all fill sizes: 1ml, 2ml and 5ml. All results were well within the specifications and demonstrate the consistent manufacture of Sealer Protein Solution.

Characterisation of Impurities
No new impurities are introduced in the manufacture of Sealer Protein Solution that do not occur in the manufacture of the drug substance.

Justification of Specification(s)
Each specification for Sealer Protein Solution is justified based on a combination of compendial limits, existing manufacturing and process development data, historical experience with Baxter’s Fibrin Sealants, process capabilities, analytical method validation data and product stability data.
Reference Standards or Materials
No primary reference standards are used in the manufacture and quality control of Sealer Protein Solution.

Container Closure System
The primary packaging for Sealer Protein Solution, Component 1 of Fibrin Sealant VH S/D Frozen, consists of one polypropylene double chamber syringe, one tip cap of the same polypropylene, which closes both cones, and two silicone rubber pistons (stoppers), one for each barrel. Both the syringes and tips comply with the requirements for containers per the current Ph. Eur. (3.1.3 Polyolefines and 3.2.2 Plastic containers and closures for pharmaceutical use) and both are sterilised by gamma irradiation. The pistons meet the chemical requirements of the current Ph. Eur. (3.1.9 Silicone Elastomer for Closures and Tubings) and are also sterilised by gamma irradiation.

Stability

Stability Summary and Conclusion
Seven lots of Sealer Protein Solution, representing all fill sizes, were entered in a long term stability study and a stability-after-thawing program according to the respective ICH-guidelines.

Real time data from long-term studies covering a storage period of 24 months for the 1ml and 5ml filling sizes and up to 18 months for the 2ml filling size at a storage temperature of ≤ -20°C have been provided. Results from these studies have indicated that all monitored parameters of all lots are well within the specifications and remained unchanged during the whole period of observation.

For stability after thawing, data for up to 72 hours storage at room temperature are available for all fill sizes. These stability studies are completed. All results remained within the range of specification during the entire storage period, thus demonstrating the unimpaired product quality of the thawed Sealer Protein Solution for up to 72 hours when stored at room temperature.

On the basis of these data the following storage conditions and shelf life for the final product Fibrin Sealant VH S/D Frozen have been proposed:
- Frozen product: Shelf life of 24 months, when stored at temperatures of ≤ -20°C
- Product after thawing: Shelf Life of 72 hours when stored at room temperature

Post-approval Stability Protocol and Stability Commitment
The ongoing stability studies examining the stability of Sealer Protein Solution for Fibrin Sealant VH S/D Frozen shall be continued post-approval as per the testing protocols provided.

APPENDICES

Facilities and Equipment
Details of product manufacturing facilities are satisfactory.
Adventitious Agents Safety Evaluation

Prion safety
In the production process of Sealer Protein VH S/D, the Fibrinogen component of Tisseel VH S/D, the manufacturing step 1, i.e. the separation of the cryoprecipitate, was found to contribute to the TSE safety profile of the product, with a log10 reduction factor of 1.8. Together with the already very low risk for plasma for fractionation, the conclusion is that the residual risk of Sealer Protein VH S/D with respect to vCJD is considered theoretical and extremely low.

Estimates for reducing vCJD infectivity of the Sealer Protein and Thrombin Components of Tisseel, and Human Serum Albumin used as an excipient, have been provided, using both published information and experimental studies. The overall risk is extremely low.

Moreover, the results of a study on the prion removal capacity of the fibrin sealer protein process have been provided (as per the commitment to the MHRA). Prion reduction factors obtained indicate a substantial prion removal capacity of the manufacturing process.

Viral safety
The collected plasma used as source material is in compliance with all European and US regulations. Each plasma donation is tested for infectious markers for HIV-1/-2, Hepatitis B and C surface antigen (HbsAg). Each single plasma donation released for further manufacturing must be non-reactive for the above markers.

Each manufacturing plasma pool is tested and released for further manufacturing only when:
- non-reactive for HIV, Hepatitis C, Hepatitis A and Hepatitis B using nucleic acid amplification techniques
- Parvovirus B19 concentration not exceeding $10^5$ IU/ml as measured by nucleic acid amplification techniques

Virus-spiking experiments have validated the efficacy of virus inactivation/removal during the whole manufacturing process. The virus inactivation/removal potential has been validated and an adequate range of challenge viruses was used in this study.

Two virus clearance steps are integrated into the manufacturing process of each component: S/D treatment and Vapour Heating. The sequence of these steps is different for sealer protein and thrombin. Eleven virus clearance studies have been undertaken for the fibrin sealant components.

All the studies were conducted in accordance with current guidance (CPMP/BWP/268/95, revised). The downscaled process was equivalent with the large scale manufacturing process. Process material from the large-scale manufacturing process was used as starting material for each study, further ensuring the validity of the laboratory downscale. Reduction factors were calculated according to current guidance. The validation studies provide assurance of the efficacy of the process for removal of viral contaminants.

REGIONAL INFORMATION
Each Fibrin Sealant VH S/D Frozen syringe is packed together with one set of sterile accessory devices, the Duo Set, designed to simultaneously apply identical amounts of
Sealer Protein Solution and Thrombin Solution. CE-mark application of the Duo Set is in preparation and the components of the Duo Set have been tested for biological safety.

The certificates of suitability for the materials used in the manufacture of fibrin sealant have been provided.

**DRUG SUBSTANCE: THROMBIN SOLUTION – FROZEN**

**General information**
A monograph for the Fibrin sealant kit is included in the European Pharmacopoeia (*Ph Eur 0903*), and thrombin is one of its components. Thrombin is a key enzyme of the blood coagulation system. It converts fibrinogen into insoluble fibrin. This process includes the enzymatic removal of fibrinopeptides A and B from fibrinogen and the activation of FXIII by thrombin resulting in the stabilization of the newly formed fibrin clot. Additionally, thrombin promotes clot formation by activating platelets via protease-activated receptors PAR1 and PAR4, which leads to fibrin binding and aggregation of these cells. By direct activation of the coagulation factors V, VIII, and XI, thrombin also enhances its own generation from prothrombin. Thrombin is converted functionally to an anticoagulant enzyme through its interaction with thrombomodulin, a molecule expressed on the surface of endothelial cells. The interaction of these two molecules is needed for the efficient activation of protein C by thrombin. Activated protein C inactivates factor Va and factor VIIIa by proteolytic cleavage, which finally results in the down modulation of procoagulant processes including thrombin generation. Besides its function as procoagulant and anticoagulant enzyme, thrombin seems to play a role in protecting the newly formed clot from fibrinolysis by activating thrombin-activatable fibrinolysis inhibitor (TAFI). Activation of TAFI is an inefficient process that requires relatively large amounts of thrombin, which are usually present in the course of the natural blood coagulation process after the clot has formed. As for protein C, this process is accelerated by the interaction of thrombin with thrombomodulin.

**Nomenclature**
INN: Human thrombin  
ATC-code: B02BC local haemostatics  
B02BD30 as blood coagulation factor

**Structure**
Satisfactory information on the structure of human thrombin has been provided from literature.

**Manufacture**

**Manufacturers**
The manufacturing sites involved in the production of Thrombin VH S/D Bulk have been satisfactorily identified.

**Description of Manufacturing Process and Process Controls**
Satisfactory description of the manufacturing process and process controls is provided. The in-process controls applied are generally appropriate and appear to give a reproducible product.
Filling, Storage & Transport
Internal transports are performed according to written procedures.
At the minimum, the following information is recorded on the labels: Product name, Resource number, Lot number and Storage temperature.
A transfer protocol containing the following information is delivered along with the transport containers: Product name, Lot number, Amount/weight, Storage temperature, Originator and Recipient Departments, Date and signature.
The eluate, portioned in labelled plastic buckets, which are closed and frozen, is transported from one manufacturing site to another manufacturing site. The portioned eluate may be stored at \(-20^\circ C\) for up to 6 months. The vapour heated Thrombin Powder and the Ultrafiltration Concentrate are filled into double polyethylene bags, which are sealed and labelled. The Ultrafiltration Concentrate may be stored at \(-20^\circ C\) for up to 12 months or at \(+2^\circ C – 8^\circ C\) for up to 7 days.

Control of Materials
Human plasma, complying with the requirements of the Ph. Eur. Monograph on Human Plasma for Fractionation (0853), and with the Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95) is used as the starting material for the manufacture of Thrombin VD S/D Bulk. In addition, the collected plasma used as source material is in compliance with all European and US regulations, certified centrally by the EMEA under the number EMEA/H/PMF/000003/2004 (updated annually most recently updated 24 April 2008).

The raw materials used in the manufacture of Sealer Protein Bulk and Drug Product comply with current compendial specifications. A supplier qualification program and regular audits have been established, and certificates of analysis have been provided. Incoming materials are tested for identity and additional tests as specified. Conductivity and bioburden of Water for injections is regularly monitored.

Controls of Critical Steps and Intermediates
The critical steps for the manufacture of Thrombin VD S/D Bulk are those contributing to significant viral reduction. Deviations from the defined limits result in an investigation according to Baxter’s established exception management process. The system ensures that deviations are duly documented and appropriate actions are initiated.

Process Validation and/or Evaluation
Two dedicated virus inactivation steps (i.e. Vapour Heat treatment and S/D treatment) have been incorporated into the manufacture of the Thrombin VH S/D Bulk. The combined use of these independent viral inactivation methods improves the viral safety margin of the product. Critical operating parameters with appropriate limits have been identified.

Three consecutive conformance lots of Thrombin VH S/D Bulk were produced according to the approved validation protocol with the established acceptance criteria. All validation activities were performed at the manufacturing scale. In process controls measured during all process steps consistently met their predetermined parameters and the quality characteristics of Thrombin VH S/D Bulk were within the established specifications. All three validation lots were within the bioburden specifications at Thrombin VH S/D Bulk level and the drug substance complied with the predetermined specifications and quality attributes. No other deviations from the validation parameters occurred.
Manufacturing Process Development
Thrombin VH S/D drug product has been developed in order to enhance viral safety and to increase purity. Two virus inactivation steps, i.e. Vapour Heat treatment and S/D treatment, were incorporated into the manufacturing process. The combined use of these independent viral inactivation methods increased the viral safety margin of the final product. Manufacturing process development focused on all process steps. Limits were identified and the influence of deviations from these limits on product quality and yield was examined.

Characterisation

Elucidation of Structure and other Characteristics
Thrombin is a serine protease of the trypsin family with a molecular weight of approximately 34kDa. It consists of two polypeptide chains, i.e. the A- and B-chain, whereby the larger B-chain carries the functional epitopes, is glycosylated, and it has the typical fold of serine proteases.

The purity and high specific activity of the thrombin fraction obtained by ion-exchange chromatography has been also examined by SDS Polyacrylamide Gel Electrophoresis (SDS-PAGE).

Impurities
Thrombin VH S/D Bulk is a human plasma-derived material, which contains thrombin as active ingredient.

Materials introduced throughout the manufacturing process for different purposes and reduced to residual levels by the subsequent process steps have been identified and listed as process-related impurities.

CONTROL OF DRUG SUBSTANCE: THROMBIN SOLUTION – FROZEN

Drug Substance Specification
The drug substance specification has been provided and is compliant with the Ph. Eur. Monograph (Fibrin Sealant Kit: 0903).

Analytical Procedures
Details of the analytical procedures have been provided. They are compendial methods and are considered appropriate.

Validation of Analytical Procedures
Validation reports for the pharmacopoeial analytical methods are not presented. The method used for the Determination of Thrombin Activity is modified from methods described in Ph. Eur. (Fibrin Sealant Kit: 0903). For this test, validation according to CPMP/ICH/381/95 and CPMP/ICH/281/95 was performed.

Batch Analyses
Results from the quality control testing of Thrombin VH S/D production scale conformance lots have been provided. All results are well within the specifications and demonstrate the consistent manufacture of Thrombin VH S/D.

Justification of Specification
The specification is based on a combination of compendial limits, existing manufacturing and process development data, toxicity studies, historical experience with Baxter’s
predecessor fibrin sealant products, process capabilities, analytical method validation data and product stability data.

**Reference Standards or Materials**
For determination of the Thrombin activity, the potency [IU] is measured using the clotting time method against the World Health Organization (WHO) International Standard for Thrombin (WHO #01/580).

**Container Closure System**
This has been adequately described and specifications of the drug substance containers have been provided. Compatibility of the container closure system with the drug substance (thrombin VH S/D Bulk) has been demonstrated by stability studies, which have confirmed the suitability of the container closure system for the storage of thrombin VH S/D Bulk.

**Stability**

**Stability Summary and Conclusions**
The data provided generally support the physicochemical and biological stability of the drug substance under the storage and handling conditions described.

**Stability Data**
Stability studies have been conducted with three conformance lots of thrombin VH S/D bulk used for production of the drug product. The stability data presented did not show any significant changes during the whole period of observation, and therefore support the shelf life proposed and confirm the suitability of the container.

Stability studies were conducted with the intermediates obtained during the manufacturing process, used for production of Thrombin VH S/D Bulk. The stability data did not show any significant changes during the whole period of observation and therefore support the shelf life proposed.

**DRUG PRODUCT: THROMBIN SOLUTION – FROZEN**

**Description and Composition of the Drug Product**
Thrombin Solution is the second component of Fibrin Sealant VH S/D Frozen, it is formulated as a sterile, non-pyrogenic, vapour heated, solvent detergent-treated, frozen solution made from pooled human plasma.
Thrombin Solution contains human plasma derived thrombin and calcium chloride as active ingredients. Thrombin functions as a coagulation factor and calcium chloride acts as a clotting activator.
Thrombin Solution is filled into one chamber of the double-chamber plastic syringe, the final container of the product. (Sealer Protein Solution, component one of Fibrin Sealant VH S/D Frozen, is filled into the other chamber of the double chamber plastic syringe.)

**Dosage Form Description**
Fibrin Sealant VH S/D Frozen consists of a double-chamber syringe containing equal volumes of the Sealer Protein Solution and of the Thrombin Solution. Each solution is filled into one chamber of the syringe. The product is available in 2ml, 4ml and 10ml
pack sizes, with the 2ml pack size containing 1ml Sealer Protein Solution and 1ml Thrombin Solution; the 4ml pack size containing 2ml of each solution, and the 10ml pack size containing 5ml of each solution, respectively. Fibrin Sealant VH S/D Frozen is thawed prior to use and then applied using the application device (Duo Set) supplied with the product.

**Pharmaceutical Development**
The development pharmaceutics were satisfactorily presented and the issues addressed include the rationale for the formulation and its subsequent evolution, and the manufacturing process development. Development studies on packaging materials were provided. Chemical and physical compatibility were demonstrated in the course of the finished product stability studies.

**Manufacture**

**Batch Formula**
The Thrombin Solution Batch formula has been provided for an average batch size.

**Description of Manufacturing Process and Process Controls**
A satisfactory account of the manufacturing process has been provided. The in-process controls applied are appropriate and meet the required acceptance criteria. Appropriate control tests are applied to the final container samples for release testing, and until the completion of tests, the final containers are quarantined.

**Control of Critical Steps and Intermediates**
The critical steps have been described.

**Process Validation and/or Evaluation**
Three conformance lots of Thrombin Solution were manufactured under validation protocol to demonstrate process consistency. In-process parameters and controls have been monitored to evaluate the reliability of the process. The process was appropriately validated and is considered capable of producing a drug product of adequate quality, conforming to predetermined parameters and acceptance criteria.

In order to demonstrate the homogeneity of the bulk solution after volume adjustment a mixing study has been performed, following specific sampling instructions, sampling schemes and acceptance criteria. Samples taken from the bottom and top layers of the vessel were analyzed for protein content. All lots evaluated in the study complied with the acceptance criteria.

Sterile Filling, Packaging and Freezing were satisfactorily validated. The validation results demonstrated that the in-process parameters and controls are within the established limits. The Thrombin Solution was validated for lot homogeneity throughout filling, for the maximum process hold time and for aseptic conditions during sterilising filtration.

Overall, the data demonstrate that the process is capable of producing bulk Sealer Protein Solution and filled containers which are homogeneous and of acceptable and consistent quality.
Control of Excipients

Specifications
All materials used in the pharmaceutical production of Thrombin Solution, i.e. Human Albumin, Sodium Chloride and Water for Injections, comply with the current edition of the Ph. Eur. Analytical procedures for the tests regarding the excipients are performed according to the requirements of the current Ph. Eur. monographs, and the specifications of the excipients are set to comply with the current edition of the Ph. Eur.

Control of Drug Product

Finished Product Specification for Thrombin Solution
The finished product specification has been provided and is compliant with the Ph. Eur. Monograph.

Analytical Procedures
Details of the analytical procedures have been provided. Most are compendial methods and are considered appropriate.

Validation of Analytical Procedures
Validation reports for the pharmacopoeial methods are not presented. The methods used for the Determination of Thrombin activity and the Determination of Protein Content are modified from methods described in Ph. Eur. (Fibrin Sealant Kit: 0903) and (2.5.33: Total Protein, method 7). For these tests, validation according to CPMP/ICH/381/95 and CPMP/ICH/281/95 was performed.

Batch Analyses
Results from the quality control testing of Thrombin Solution production scale conformance lots were provided for all fill sizes: 1ml, 2ml and 5ml. All results were well within the specifications and demonstrate the consistent manufacture of Thrombin Solution.

Characterisation of Impurities
No new impurities are introduced in the manufacture of Thrombin Solution that do not occur in the manufacture of the drug substance.

Justification of Specification(s)
Each specification for Thrombin Solution is justified based on a combination of compendial limits, existing manufacturing and process development data, historical experience with Baxter’s Fibrin Sealants, process capabilities, analytical method validation data and product stability data.

Reference Standards or Materials
See drug substance above.

Container Closure System
Identical to Sealer Protein Solution above.
Stability

Stability Summary and Conclusion
Seven lots of Thrombin Solution, representing all fill sizes, were entered in a long term stability study and a stability-after-thawing program according to the respective ICH-guidelines.

Real time data from long-term studies covering a storage period of 24 months for the 1ml and 5ml filling sizes and up to 18 months for the 2ml filling size at a storage temperature of \( \leq -20^\circ\text{C} \) have been provided. Results from these studies have indicated that all monitored parameters of all lots are well within the specifications and remained unchanged during the whole period of observation.

For stability after thawing, data for up to 72 hours storage at room temperature are available for all fill sizes. These stability studies are completed. All results remained within the range of specification during the entire storage period, thus demonstrating the unimpaired product quality of the thawed Thrombin Solution for up to 72 hours when stored at room temperature.

Post-approval Stability Protocol and Stability Commitment
The ongoing stability studies examining the stability of Thrombin Solution for Fibrin Sealant VH S/D Frozen shall be continued post-approval as per the testing protocols provided.

APPENDICES

Facilities and Equipment
Details of product manufacturing facilities are satisfactory.

Adventitious Agents Safety Evaluation
Prion safety
A number of steps have been identified, where TSE removal is reported, or which would be expected to contribute to the removal of TSE agents. Experiments performed and published data have provided the prion reduction factors for these steps. These reduction factors together with the already very low risk for plasma for fractionation indicate that the residual risk of Thrombin VH S/D with respect to vCJD is considered theoretical and extremely low.

Viral safety
See Sealer Protein Solution above.

EXCIPIENT: HUMAN ALBUMIN

General information
Partially Stabilised Human Albumin Bulk Solution (PSHABS) is manufactured from coagulation factors-depleted human plasma fractionated according to the COHN method from plasma complying with the monographs of "Annex to the EC guide to GMP Manufacture of Products Derived from Human Blood or Human Plasma" (as published:III/5717/99-en) and "Human Plasma for Fractionation“ (Ph.Eur. 0853). Each single plasma donation can be classified as "Source Plasma" complying with CFR 21, §
640.60 - § 640.76 and/or "Plasma, Fresh Frozen" and "Plasma, Frozen" complying with the regulations of the WHO Expert Committee on Biological Standardisation, Technical Report Series 840 (1994). Only Human Albumin Solution that has been batch released by an Official Control Authority (OCABR) will be used in the manufacture of Tisseel VH S/D.

Manufacture

Manufacturers
The manufacturing sites involved in the production of Albumin Bulk Solution have been satisfactorily identified.

Description of Manufacturing Process and Process Controls
Satisfactory description of the manufacturing process and process controls is provided. The in-process controls applied are generally appropriate and appear to give a reproducible product.

Control of Materials
All details concerning the processing of human plasma used for the manufacture of the Partially Stabilized Human Albumin Solution (PSHABS) are described in the “Plasma Master File – Collection and Control of Starting Materials for the Production of Blood Derivatives. This PMF is approved via the central route by the EMEA under the number EMEA/H/PMF/000003/04 (updated annually most recently updated 24 April 2008). All reagents are from qualified suppliers and are of pharmacopoeial grade.

Controls of Critical Steps and Intermediates
The critical step for the manufacture of PSHABS has been identified and it is critical with respect to its potential capacity to inactivate/remove human pathogenic viral contaminations. The in-process parameters defined for this step have been demonstrated and ensure the consistency of the process and the effectiveness in virus inactivation/removal.

Process Validation
The manufacturing procedure has been performed by the manufacturing site for many years. Comparative batch release data show the consistency of the manufacturing procedure and demonstrate that the set release limits are constantly met.

Characterisation

Impurities
Materials introduced throughout the manufacturing process for different purposes and reduced to residual levels by the subsequent process steps have been identified and listed as process-related impurities.
CONTROL OF DRUG SUBSTANCE: HUMAN ALBUMIN

Drug Substance Specification
The drug substance specification has been provided.

Analytical Procedures and their Validation
The analytical procedures used to analyse the release parameters of Partially Stabilised Human Albumin Bulk Solution are performed in accordance with the current edition of the Ph Eur. In the course of validation, every method was tested for its routine suitability.

Batch Analyses
Results from the quality control testing of human albumin (partially stabilised) bulk solutions have been provided. All results are well within the specifications and demonstrate the consistent manufacture of PSHABS.

Justification of Specification
The specification is has been adequately justified.

Container Closure System
This has been satisfactorily described.

Stability
Long-term stability studies have been conducted with three batches each of two intermediates of the manufacturing process of albumin bulk solution. For the stability tests samples have been stored in containers equivalent to the containers used in production and testing is performed using the same test methods as those described for analytical tests on drug substance and drug product. In all of the batches investigated, composition, purity and safety of the intermediates were unimpaired throughout the testing period and support the proposed storage conditions and duration of storage to be permitted before retesting.

Long-term stability studies have also been performed with four batches of bulk solution and the data meet the set specifications, therefore supporting the proposed storage conditions and duration of storage before retesting.

DRUG PRODUCT: HUMAN ALBUMIN

Description and Composition of the Drug Product
Human Albumin Solutions are sterile aqueous solutions. They are clear, slightly viscous solutions, and the colour varies from colourless, yellow to brown or green. The composition of the drug product has been provided.

Pharmaceutical Development
Human albumin is produced by Cohn fractionation.

Manufacture

Description of Manufacturing Process and Process Controls
A satisfactory account of the manufacturing process has been provided. The in-process controls applied are appropriate and meet the required acceptance criteria.
Control of Critical Steps and Intermediates
The critical steps have been described.

Process Validation and/or Evaluation
For sterilisation and filling, routine methods are used which are in accordance with GMP guidelines for biological products and parenteral products that are not sterilised in final containers. These methods are also regularly used for other products and have been previously validated. They are consistently checked by in-process controls, and no further validation data have been presented.

Control of Excipients

Specifications
The excipients used in the formulation of Human Albumin, i.e. Sodium caprylate, Sodium N-acetyltryptophanate, and Sodium Chloride comply with the current edition of the Ph Eur.

Control of Drug Product

Finished Product Specification for Thrombin Solution
The specification for Human Albumin has been provided and is compliant with the Ph. Eur. Monograph.

Analytical Procedures and their Validation
The analytical procedures used to analyse the release parameters of Human Albumin are performed in accordance with the current edition of the Ph. Eur. In the course of validation, every method was tested for its routine suitability.

Batch Analyses
Results from the quality control testing of three batches of Human Albumin have been provided. All results were well within the specifications and demonstrate the consistency of the manufacturing process.

Characterisation of Impurities
Human Albumin Solution is a human plasma-derived material that contains a high amount of human albumin according to Ph. Eur. requirements. Other proteins originating from human plasma are part of the preparation and have been identified as product-related substances.
Materials introduced throughout the manufacturing process for different purposes and reduced to residual levels by the subsequent process steps have been identified and listed as process-related impurities.

Justification of Specification(s)
The specification complies with the Ph. Eur. Monograph for Human Albumin Solution <0255>.

Reference Standards or Materials
International Prekallikrein Activator Standard and Human Albumin for Electrophoresis Reference Preparations used.
Container Closure System
Vials of siliconised or alternatively non-siliconised, surface-treated soda-lime-silica glass, hydrolytic type II are used as primary packaging material for Human Albumin, sizes 70ml and 125ml. These containers meet the requirements for Type II glass of the current Ph. Eur.3.2.1. “Glass Containers for Pharmaceutical Use” and current USP <661> “Containers”. In addition Baxter test the containers for identity. Before use vials are either siliconised or used without being siliconised, sterilised in a sterilisation tunnel by heating to NLT 250°C for at least 6 minutes. The closures are of halogenobutyl rubber quality and meet the chemical requirements of the current Ph. Eur. 3.2.9. “Rubber Closures for Containers for Aqueous Preparations for Parenteral Use” and of the current USP <381> “Elastomeric Closures for Injections”.

Stability

Stability Summary and Conclusion
For Human Albumin real time data for 60 months of storage at +10°C have been provided. The stability studies were performed on batches filled in siliconised and in nonsiliconised glass vials. In all batches investigated, the stability indicating parameters were stable throughout the testing period (5 years) at +10°C and support the proposed shelf-life and storage conditions of 5 years when stored at +2°C and +8°C.

ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Summary of Product Characteristics
The SPC is satisfactory.

Patient Information Leaflet
The PIL is satisfactory. The results of the user readability are satisfactory.

Labels
The labels are satisfactory.

Comment on Expert report
The expert report was prepared by a regulatory consultant with appropriate experience.

MAA form
The MAA is satisfactory.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
With respect to the quality dossier the application for Tisseel is approvable.

The expert reports are of sufficient quality with regard to current European Regulatory requirements.

There are no pharmaceutical objections to the grant of a marketing authorisation.
INTRODUCTION

This is an abridged standard national application for TISSEEL Ready to use. TISSEEL VH Fibrin Sealant kit has been licensed in the UK since May 2000 (PL 00116/0321). TISSEEL VH Fibrin Sealant mimics the final stage of the blood coagulation cascade using high concentrations of fibrinogen and thrombin.

Fibrin Sealant, Vapour Heated, Solvent/Detergent Treated (TISSEEL Ready to use) is a further development of the currently licensed product TISSEEL VH Fibrin Sealant Kit (PL 00116/0321). Viral inactivation steps are included in the manufacturing process of both TISSEEL VH Fibrin Sealant Kit and TISSEEL Ready to use to address the potential for transmission of viral pathogens. TISSEEL VH Fibrin Sealant Kit incorporates a single viral inactivation step, vapour heat treatment, while TISSEEL Ready to use incorporates two distinct viral inactivation procedures, vapour heat treatment and solvent/detergent treatment. Solvent/detergent treatment of both biological components of TISSEEL Ready to use, specifically Sealer Protein Concentrate (Human) and Thrombin (Human), provides an increased margin of safety relative to TISSEEL VH Fibrin Sealant. The solvent/detergent treatment is well defined and proven to be highly effective in inactivating lipid-enveloped viruses. It has been widely used for virus inactivation of plasma-derived proteins.

Additionally, the handling properties of the Sealer Protein component and the purity of the Thrombin component have been improved.

TISSEEL VH Fibrin Sealant is currently available only in lyophilized form, which requires reconstitution of the two biological components prior to product application. TISSEEL Ready to use will be available both in a frozen and lyophilized form with the compositions of the final, ready-to-use Sealer Protein and Thrombin Solutions being identical for both of these presentations.

The approved indication for TISSEEL VH is for supportive treatment, where standard surgical techniques are insufficient, for:

- for improvement of haemostasis
- as a tissue glue to promote adhesion/sealing or as suture support:
  - in gastrointestinal anastomoses
  - in neurosurgery where contact with cerebro-spinal fluid or dura mater can occur.

TISSEEL Ready to use (frozen and lyophilized) is intended to be effective for the same indications (specified above) as the currently licensed product in the UK Tisseel Kit (VH), Two-Component Fibrin Sealant (PL 00116/0321).
NON-CLINICAL ASSESSMENT

Overview of Nonclinical Testing Strategy
The development plan for TISSEEL Ready to use, also called TISSEEL VH S/D (frozen and lyophilized) throughout this report, was designed to demonstrate bio-equivalence to TISSEEL VH. Non-clinical testing focused on efficacy, safety, toxicity and mutagenicity. All in vitro and in vivo studies are conducted according to current GLP regulations.

Pharmacology
Comparative in vivo studies were performed to evaluate the bio-equivalence of TISSEEL Ready to use (frozen and lyophilized) and TISSEEL VH. In order to investigate primary, secondary and sustained haemostatic and sealing efficacy in different animal species the following animal models were applied:

- Partial Rat Kidney Resection Model
- Rabbit Liver Abrasion Model
- Rabbit Liver Resection Model with Acute Hyperfibrinolysis
- Rabbit Partial Lung Resection Model

The data from these studies demonstrate:

- TISSEEL VH S/D (frozen and lyophilized) is as safe and effective as TISSEEL VH for use as a haemostatic agent in the partial rat kidney resection model.
- TISSEEL VH S/D (frozen and lyophilized) and TISSEEL VH show an excellent ability to sustain haemostasis over a 24 hour period in a rabbit liver abrasion model with no statistical difference between the products.
- TISSEEL VH S/D (frozen and lyophilized) and TISSEEL VH reveal no statistically significant differences in blood loss in a rabbit liver resection model with acute hyperfibrinolysis.
- TISSEEL VH S/D (frozen) is as effective as TISSEEL VH for use as a haemostatic agent in a rabbit liver abrasion model.
- TISSEEL VH S/D (frozen and lyophilized) is as effective as TISSEEL VH for use as a sealing agent in the rabbit lung resection model

In summary, in vivo studies performed in different animal species demonstrate the bio-equivalence of TISSEEL VH S/D (frozen and lyophilized) and TISSEEL VH.

Pharmacokinetics
TISSEEL VH S/D (frozen and lyophilized) is intended for local application only, therefore systemic exposure or distribution to other organs and tissues is not expected and Pharmacokinetic Studies were not conducted.

Toxicology
Two single dose toxicity studies of TISSEEL Ready to use (frozen) and TISSEEL VH were conducted, using six rats and rabbits per product in each respective study. In both
studies, an amount of 5mL/kg was injected subcutaneously. The dose was chosen based on the assumption that a patient (80 kg bodyweight) would receive a maximum of 40mL of Fibrin Sealant (typically 2-10 mL) and a tenfold higher amount (400mL=5mL/kg) was tested in the animals. The single dose toxicity studies comparing TISSEEL Ready to use (frozen) and TISSEEL VH revealed no overt signs of toxicity or macroscopic changes of the organs and therefore indicated no acute toxicity.

Although not necessarily needed for plasma-derived products, two in vitro mutagenicity studies using *Escherichia coli* reverse mutation assay were performed with the Sealer Protein and Thrombin solutions of TISSEEL Ready to use (frozen). Neither cytotoxic nor genotoxic effects occurred up to a maximum dose of 100000 µl/plate. Therefore, TISSEEL Ready to use is considered to be non-mutagenic.

Local tolerance was evaluated in two comparative in-vivo studies performed in rats and rabbits using a subcutaneously implanted spongiosa block model. In the rat study there was no statistically significant difference between TISSEEL Ready to use (frozen) and TISSEEL VH in regards to granulation tissue formation, residual fibrin, inflammation and foreign body reaction. No animal had more than a mild foreign body reaction with any of the preparations. However, human fibrin injected into animals represents a heterologous protein and some reaction is to be expected. TISSEEL Ready to use (frozen) demonstrated trendwise less inflammatory response than TISSEEL VH, but in both products responses were mild to medium. Some inflammatory reaction is also expected as a natural part of the wound healing process. In the rabbit, more fibrin remained due to its lower fibrinolytic activity. Neither fibrin sealant preparation revealed any significant local intolerance with foreign body reaction. A minor to medium inflammation, which is a normal part of the natural fibrin degradation and beginning of wound healing, was observed. Remaining fibrin was indirectly proportional with granulation tissue formation, but no significant differences were found between the two Fibrin Sealant preparations.

The cellular compatibility of TISSEEL Ready to use (frozen and lyophilized) and TISSEEL VH was compared using human fibroblasts in cell culture. This test system has previously been shown sufficiently sensitive to detect differences in cellular compatibility between fibrin sealant preparations. Cytotoxic cell changes were noted in the control preparation, but not in fibroblasts treated with TISSEEL Ready to use (frozen and lyophilized) and TISSEEL VH. All test fibrin sealant preparations therefore showed cellular compatibility and could not be differentiated from each other. These data suggest that TISSEEL Ready to use and TISSEEL VH are biologically equivalent with respect to cellular compatibility.

**Toxicology of excipients and residual solvents: literature based risk assessment**

The new fibrin sealant preparation TISSEEL Ready to use (frozen and lyophilized) contains a number of components not present in TISSEEL VH: L-histidine, niacinamide, polyethylene glycol 4000 (PEG 4000), Tri-n-butyl phosphate (TNBP), octoxynol-9 (Triton X-100), and L-lysine. Polysorbate 80 (Tween 80) is present in both preparations, however, higher concentrations are used in TISSEEL Ready to use.

Histidine is added during preparation of the Sealer Protein Bulk Solution prior to lyophilization and vapour heat treatment. Histidine has a stabilizing effect on the Sealer
Protein during vapour-heat treatment. Niacinamide is used during pharmaceutical formulation of TISSEEL Ready to use to lower the viscosity of the Sealer Protein Solution. Niacinamide also significantly facilitates the reconstitution of the Sealer Protein Concentrate (Sealer Protein Drug Product of the lyophilized formulation of TISSEEL Ready to use).

Lysine is added during purification of the Sealer Protein Drug Substance in order to reduce the plasminogen content. Lysine is present in trace amounts in the final product.

TNBP, octoxynol-9, and polysorbate 80 are used in the S/D viral inactivation treatment of plasma-derived products and are components of the solvent detergent mixture in the production of Sealer Protein and Thrombin Drug Products.

Polyethylene glycol (PEG) is used in the production of Sealer Protein Drug Substance as a precipitating agent.

The quantities of these substances present in a presumed maximum applied dose (40mL) of TISSEEL Ready to use (frozen and lyophilized), as well as the amount per kg body weight that would be received by a 70 kg individual given the maximum dose of 40mL are summarized in Table 2.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Maximum quantities in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>per 40 mL</td>
</tr>
<tr>
<td>Histidine</td>
<td>500</td>
</tr>
<tr>
<td>Niacinamide</td>
<td>180</td>
</tr>
<tr>
<td>Lysine</td>
<td>≤ 8</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>≤ 20</td>
</tr>
<tr>
<td>TNBP</td>
<td>≤ 0.12</td>
</tr>
<tr>
<td>Octoxynol-9</td>
<td>≤ 0.26</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>≤ 43</td>
</tr>
</tbody>
</table>

Table 1. Estimated Maximum Level of Use

Histidine, Niacinamide and Lysine
Histidine, niacinamide, and lysine are naturally occurring substances found in animals and the human body.

Histidine
Histidine, an essential amino acid, is administered for therapeutic purposes as infusion solutions of amino acid mixtures. Subjects presenting with catabolic conditions receive intravenous doses of up to 197.4 mg/kg or 13.8 g in a 70 kg subject.

Niacinamide
Niacinamide (vitamin B3, vitamin PP) is a water-soluble B vitamin found primarily in products of animal origin. The daily requirement for adults is 15-18 mg niacin equivalents. Typical treatment doses for deficiency are 500 mg, which corresponds to 6.25 mg/kg for 80 kg person. Topical application of 4% niacinamide gel is well tolerated and safe in humans.
Lysine
Lysine is an essential amino acid for humans and has been used for numerous therapeutic indications. The normal plasma concentration is between 29.3 to 25.4 mg/L. The daily adult requirement is in the range of 17 to 36 mg/kg/d. The amount of histidine (500 mg or 7.1 mg/kg), niacinamide (180 mg or 2.6 mg/kg), and lysine (≤8 mg or ≤0.1 mg/kg) delivered in a theoretical maximum dose of 40 mL TISSEEL Ready to use (frozen and lyophilized) for a 70 kg individual would not be expected to present any risks to human health.

Tri-n-butyl phosphate (TNBP)
Based on the theoretical maximum human dose of 40 mL TISSEEL Ready to use, TNBP levels would not exceed 0.12 mg or 0.002 mg/kg. Considering the TNBP doses used in the animal experiments, no acute toxicity reactions are to be expected in the course of treatments with TISSEEL Ready to use (frozen and lyophilized).

Triton X-100 (Octoxynol-9)
Octoxynols are used as detergents, emulsifiers, wetting agents, defoaming agents, etc. Octoxynol-9, the compound with 9 repeating ethoxy groups, is a spermaticide. Octoxynols of various chain lengths as well as octoxynol salts and organic acids function in cosmetics either as surfactants-emulsifying agents, cleansing agents, solubilizing agents, or hydrotropes in a wide variety of cosmetic products at concentrations ranging from 0.0008% to 25%, with most less than 5.0%.

Octoxynol-9 is used as a detergent in the S/D viral inactivation treatment in the production of Sealer Protein and Thrombin Drug Substances.

The available clinical and non-clinical data suggest that the amounts of octoxynol-9 (≤0.26 mg or ≤0.004 mg/kg), present in a theoretical maximum 40 mL dose of TISSEEL Ready to use (frozen and lyophilized) for a 70 kg individual would not be expected to present any risks to human health.

Tween 80 (Polysorbate 80)
Polysorbate 80 is a nonionic surfactant widely used as an additive in foods, pharmaceutical preparations, and cosmetics as an emulsifier, dispersant, or stabilizer. Polysorbate 80 facilitates the dissolution of the Sealer Protein Bulk Powder during pharmaceutical formulation and improves the solubility of the Sealer Protein Concentrate (Sealer Protein Drug Product of the lyophilized formulation of TISSEEL Ready to use) upon reconstitution with Fibrinolysis Inhibitor Solution. Polysorbate 80 has been used as excipient in the Sealer Protein Concentrate of the licensed Tisseel VH product. Polysorbate 80 is also a component of the solvent detergent mixture used in the S/D viral inactivation treatment in the production of Sealer Protein and Thrombin Drug Substances.
Based on the animal and human data reviewed, the amount of Tween 80 (≤43 mg or ≤0.6 mg/kg) present in a theoretical maximum dose of 40 mL TISSEEL Ready to use (frozen and lyophilized) for a 70 kg individual would not be expected to present any risks to human health.
PEG 4000
PEG is used in cosmetics, as a vehicle for water-soluble medicines, as an ointment base, in suppositories, and as a food additive. PEG is contained in drinking fluids and solutions for intestinal lavage, as well as products for intravenous administration. Based on the data reviewed the amount of PEG 4000 (≤ 20 mg or ≤ 0.3 mg/kg) present in a theoretical maximum of 40mL TISSEEL VH SD (frozen and lyophilized) given to a 70 kg individual would not be expected to present any risks to human health.

Conclusion
TISSEEL Ready to use is a human plasma-derived biological product developed by Baxter for use for local administration in support of haemostasis and sealing. The main active ingredients (fibrinogen and thrombin) are supplied as two frozen or lyophilized components, which are identical in their composition. They are mixed in equal proportions, producing a viscous fibrin sealant that sets within a few seconds into a white clot with high tensile strength and elasticity. TISSEEL Ready to use (frozen and lyophilized) is manufactured using both vapour heat treatment and solvent/detergent (S/D) treatment as two independent viral inactivation steps, and represents an improvement over the currently available licensed Baxter fibrin sealant manufactured with only the vapour heat treatment for virus inactivation.

Numerous studies have demonstrated the safety and efficacy of currently licensed Baxter fibrin sealant.

The focus of the present documentation was to show that the addition of this virus inactivation step does not impair the quality of the product (regarding efficacy, toxicity and tolerance). Therefore, in most of the studies described here, TISSEEL Ready to use (frozen, lyophilized or both forms in parallel) was tested in comparison with the currently licensed product TISSEEL VH Fibrin Sealant. All studies were conducted in compliance with GLP-requirements.

The second goal of this documentation was to highlight the published literature that demonstrates the non-toxicity of the excipients and the residuals of solvent/detergent reagents. (L-histidine, niacinamide, L-lysine, polyethylene glycol 4000 [PEG 4000], tri-n-butyl phosphate [TNBP], Triton X-100 [Octoxynol-9], and Tween [Polysorbate] 80).

Pharmacodynamic in vivo studies in four animal models closely imitating the situation in patients were used to investigate the indications: haemostasis and sealing. In these models, TISSEEL Ready to use and TISSEEL VH demonstrated equal efficacy regarding primary, secondary and sustained haemostasis and sealing.

Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of TISSEEL Ready to use and TISSEEL VH.

In two E. coli reverse mutation assays, no evidence for mutagenicity was shown.

TISSEEL Ready to use and TISSEEL VH were well tolerated in wound healing models in rats and rabbits.

The Sealer Protein Solutions of TISSEEL Ready to use and TISSEEL VH were also equally well tolerated by in vitro human fibroblast cultures demonstrating excellent cellular compatibility and non-cytotoxicity.
Based on a detailed literature review, the potential health hazard of the residual solvent/detergent reagents in TISSEEL Ready to use is considered to be minimal.

In summary, the in vitro and in vivo studies performed in different species provided evidence for the efficacy and safety of TISSEEL Ready to use.

ENVIRONMENTAL RISK ASSESSMENT

The applicant has not submitted a conventional ERA. No special environmental risk assessment is required because the disposal of the product does not include any potential risk for the environment. Furthermore no GMOs are contained in the product.

Since the active constituents are naturally occurring substances and the excipients are all commonly used compounds, the product is not considered to present a risk to the environment.

NON CLINICAL OVERVIEW

The non-clinical overview has been written by suitably qualified experts.

SmPC

This is acceptable.

CONCLUSION

There are no preclinical objections to the grant of this application.
CLINICAL ASSESSMENT

INTRODUCTION
This is an abridged standard national application for TISSEEL Ready to use intended for epilesional use. The product is presented as a sealant solution in a pre-filled syringe. The application is submitted under article 8.3 of Directive 2001/83/EC as amended. This application is a line extension to the currently licensed product Tisseel Kit (VH), Two-Component Fibrin Sealant (PL 00116/0321), and is an updated frozen version of the cross-referred product.

Fibrin sealants are composed of two essential ingredients: thrombin and fibrinogen, which both promote hemostasis. Fibrin Sealant Vapour Heated Solvent/Detergent Treated (FS VH S/D) is a plasma-derived, double virus inactivated fibrin sealant for topical application developed to promote hemostasis and tissue sealing/adhesion. It is the new generation product to succeed Baxter’s Vapour Heated Fibrin Sealant currently licensed in the UK under the brand name Tisseel Kit (VH), Two-Component Fibrin Sealant (PL 00116/0321). The fibrinogen content and thrombin concentration of FS VH S/D are unchanged from the currently licensed product.

TISSEEL Ready to use comprises four main constituents, which are Sealer Protein VH S/D Lyophilized (human), Thrombin VH S/D Lyophilized (human), Aprotinin (Bovine) Solution and Calcium Chloride Solution. Throughout the dossier the new product is referred to as Fibrin Sealant Vapour Heated Solvent/Detergent treated, Fibrin Sealant VH S/D lyophilized and FS VH S/D.

Baxter Healthcare Ltd. has submitted an application for a type II variation to Tisseel Kit (PL00116/0321) due to the introduction of a second virus inactivation step (S/D), which was carried out in order to comply with the current CHMP guidelines. In this application the MAH is seeking approval for the consequential changes to the registered details.

The sponsor has stated that Non-inferiority of the new Fibrin Sealant VH S/D Kit to Baxter’s predecessor product Tisseel Kit, currently licensed under marketing authorization PL 00116/0321, has been demonstrated in clinical and preclinical studies. Therefore, the indications for which the predecessor product is currently licensed are also claimed for Fibrin Sealant VH S/D Kit. In support of this claim, the MAH has submitted the results of the studies conducted during the development program for FS VH S/D, which comprise 3 studies. Two studies (Baxter clinical studies 550003 and 550001) were conducted in a hemostasis indication, the 3rd study (Baxter clinical study 550002) investigated sealing after axillary lymph node dissection.

Study 550003 is the pivotal study of the development program FS VH S/D and the required comparative trial demonstrating non-inferiority of FS VH S/D in terms of efficacy to the VH treated predecessor product as marketed in the UK (Fibrin Sealant VH). In this study, the haemostatic efficacy of FS VH S/D was evaluated in subjects undergoing cardiovascular surgery involving cardiopulmonary bypass.
Background and Overview

Baxter has requested for the current variation as a result of the two independent virus inactivation steps additional to the Virus inactivation – vapour heated over their currently available Fibrin sealant TISSEEL kit.

The sponsor has stated that vapour heated treatment is highly effective against a broad spectrum of viruses, including non-enveloped viruses such as HAV that are not affected by the proposed viral inactivation treatment, as well as lipid-enveloped RNA and DNA viruses such as HIV, HBV and HCV. The two active ingredients of fibrin sealant, fibrinogen and thrombin, are manufactured from pooled human plasma. The sponsor has stated that the new generation product FS VH S/D has been developed to further increase viral safety, by the addition of the S/D treatment step.

Indications

The approved indication for TISSEEL VH is for supportive treatment, where standard surgical techniques are insufficient, for:
- The improvement of haemostasis
- As a tissue glue to promote adhesion/sealing or as suture support:
  - in gastrointestinal anastomoses
  - in neurosurgery where contact with cerebro-spinal fluid or dura mater can occur.

Dose and dose schedule

The use of TISSEEL Ready to use is restricted to experienced physicians.

Posology:

The amount of TISSEEL Ready to use to be applied and the frequency of application should always be oriented towards the underlying clinical needs of 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.

To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the mixed Sealer Protein - Thrombin Solutions, or of the individual components, should be applied.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 4 to 20 ml. For some procedures, larger volumes may be required.

The initial amount 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.

As a guideline for the gluing of surfaces, 1 pack of TISSEEL Ready to use 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm².
CLINICAL PHARMACOLOGY

The Type II Variation is based on the Note for Guidance on the Clinical investigation of plasma-derived fibrin Sealant/ Haemostatic products (CPMP/BPWG/1089/00).

As this product is modified, the NfG requires one well-designed, comparative study with appropriate end points demonstrating support of haemostasis or reliable action as tissue glue.

The applicant has conducted three clinical studies with FS VH S/D, all of which are in different indications. Two studies (Baxter clinical studies 550003 and 550001) were conducted in a hemostasis indication, the 3rd study (Baxter clinical study 550002) investigated sealing after axillary lymph node dissection.

Because FS VH S/D is a topical haemostatic agent applied locally to treatment sites to form an elastic fibrin clot, classical pharmacokinetic or pharmacodynamic analyses are not applicable.

EFFICACY

Study 550003 (Pivotal study)

Study Objectives
To demonstrate that the haemostatic efficacy of FS VH S/D is not inferior to the haemostatic efficacy of Fibrin Sealant VH Haemostasis in cardiovascular surgery involving cardiopulmonary bypass

The primary efficacy endpoint of this study was the proportion of subjects who, after application of either FS VH S/D or TISSEEL VH Fibrin Sealant, achieved haemostasis at the primary treatment site within five minutes of treatment and maintained haemostasis at the primary treatment site until closure of the surgical wound.

Secondary efficacy endpoints included: time to haemostasis at the primary treatment site following treatment with investigational product; amount, type, and frequency of blood products received intra-operatively through 48 hours postoperative; incidence of re-bleeding at the primary treatment site following determination of haemostasis and prior to closure of the surgical wound; volume of postoperative chest tube drainage at 0, 2, 4, 6, 8, 10, 12, 16, 20, 24 and 48 hours or at time of removal, whichever occurred first; incidence of re-sternotomy for bleeding; incidence of mortality within 30 days postoperative, or at any time during hospitalization, for the cardiac surgery for which the subject was randomized and treated under this protocol; and time to hospital discharge.

Study design
Multicentre, phase 3, prospective, randomized (1:1), parallel group, double-blind study, in 21 centres and lasted from (Sept. 2002 – Nov. 2004) comparing the efficacy and safety of FS VH S/D with TISSEEL VH fibrin sealant in subjects of either gender, who were > 18 years of age, and who were scheduled to undergo re-operative cardiac surgery requiring CPB and median sternotomy or were to undergo primary CABG surgery requiring CPB and median sternotomy and had an increased risk for bleeding. Subjects
were randomized on the day of surgery, prior to the scheduled cardiac redo, or primary CABG procedure. The amount of FS VH S/D applied to the primary treatment site, and any additional bleeding sites, was determined by the investigator on a case-by-case basis. Up to 3 packages of FS VH S/D could be used per treated subject; the maximum possible dose of FS VH S/D was 12mL. The mode of administration was topical application with either the DUPLOJECT Dual Syringe Applicator.

Statistical analyses were performed as described in the *a priori* Statistical Analysis Plan. Test subjects in whom the adequacy of the mechanical blinding procedure was assessed were not included in the efficacy analysis. For the primary efficacy analysis, the proportion of subjects in each of the two treatment groups who, after application of either FS VH S/D or Fibrin Sealant VH, achieved and maintained haemostasis at the primary treatment site within 5 minutes of treatment and maintained haemostasis at the primary treatment site until closure of the surgical wound was compared using a one-sided 97.5%, non-inferiority confidence interval (CI). To demonstrate non-inferiority this CI should lie completely above the limit –δ. The value for δ was chosen to be 15% in the protocol and was confirmed, according to a pre-defined procedure, following a blinded interim calculation of the success rate for the pooled ITT population after 205 patients had been treated. The primary efficacy analysis planned consisted of only on the intent-to-treat population. (The intent-to-treat population consists of all non-Test Subjects with an observed primary endpoint). In addition to this, an efficacy analysis was planned for those subjects deemed evaluable per protocol (i.e., met all inclusion/exclusion criteria, randomized and treated correctly, and adhered to study procedures).

Upon completion of the application of FS VH S/D or TISSEEL VH fibrin sealant to all eligible bleeding sites, the time to haemostasis was monitored. Haemostasis being the point at which the surgeon visually determined all bleeding sites treated with investigational product which were controlled and did not need to be revisited to control bleeding by any other means prior to closure of the surgical wound. Subjects in whom haemostasis was not achieved within 5 minutes after application of investigational product and maintained until closure of the surgical wound, were deemed treatment failures. For any subject deemed a treatment failure, the surgeon used additional and necessary methods, which included re-application of the same investigational product to which the subject was originally randomized in order to control bleeding. All subjects receiving investigational product, including those deemed treatment failures, will complete all postoperative assessments.

**Results**

**Efficacy analysis**

The primary efficacy analysis was conducted using a one-sided 97.5% confidence interval on the difference in the proportion of subjects treated with FS VH S/D or Fibrin Sealant VH who achieved haemostasis at the primary treatment site within 5 minutes of treatment and maintained haemostasis until closure of the surgical wound, with a lower confidence bound δ of 15%.

A total of 371 patients were randomised in 21 centres, all in the US. The number of patients randomised at each site ranged from 1 to 43. The disposition of patients is
presented in the table below. (A total of 29 patients were designated test subjects and these patients were excluded from the efficacy analysis).

All patients in the ITT population were included in the analysis of the primary efficacy endpoint however a total of 29 test subjects were excluded from the ITT population. The ITT population consisted of all randomized and treated non-test subjects with an observed primary endpoint. In order to ensure that the exclusion of test subjects did not introduce bias into the analysis of study 550003, the applicant also repeated the analysis of the primary endpoint for the following populations:

- all randomized treated patients including test patients (317 patients) allocated to treatment groups as randomized;
- all randomized treated patients including test patients (317 patients) allocated to treatment groups according to treatment actually received.

\(^a\) Five subjects did not receive the treatment to which they had been randomized: 2 subjects randomized to TISSEEL VH Fibrin Sealant (Subject 160001, a test subject and Subject 270034) actually received FS VH S/D; and 3 subjects randomized to FS VH S/D (Subject 210019, Subject 210024, and Subject 260009) actually received TISSEEL VH Fibrin Sealant. Therefore, the actual number of treated subjects was 157 for FS VH S/D and 160 for TISSEEL VH Fibrin Sealant.
In all additional analyses the assessments of non-inferiority show consistent results with the original ITT and PP analyses.
The table below presents the results of the analysis of the primary efficacy endpoint for both the ITT and PP populations. For both populations the lower limit of the 97.5% CI is well above the -15% level specified as indicating non-inferiority of FS VH S/D compared to Tisseel VH.

| Summary of Primary Efficacy Endpoint for Intent-To-Treat and Per Protocol Subjects |
|-----------------------------------------------|-----------------|------------------|
| | Intent-To-Treat Subjects | Per Protocol Subjects |
| Proportion achieved hemostasis [n/N (%)] |  |  |
| FS VH S/D | 127/144 (88.2 %) | 108/123 (87.8 %) |
| TISSEEL VH | 129/144 (89.6 %) | 122/135 (90.4 %) |
| Difference in proportions, FS VH S/D minus TISSEEL VH | -1.4 % | -2.6 % |
| Standard error of the difference | 3.70 % | 3.89 % |
| Lower 97.5% one-sided CI on the Difference in Proportions | -8.6 % | -10.2 % |

**Safety analysis**
All subjects who received investigational product were to be included in the safety analysis. The primary safety endpoint was a comparison of the proportion of subjects with AEs classified as possibly or probably related to use of investigational product compared between treatment groups.

An overview of all AEs recorded during Baxter clinical study 550003 is presented in Table 14.3.1-1 according to serious/non-serious classification, severity (mild, moderate or severe) and causality (unrelated, possibly related or probably related). Of the 157 subjects treated with FS VH S/D, 76.4% (120) subjects reported 1 or more AEs; a total of 529 AEs were recorded for the 157 FS VH S/D-treated subjects. Specifically, 144 AEs in 45.2% (71/157) of FS VH S/D-treated subjects were considered serious and 385 AEs in 68.2% (107/157) of subjects were considered non-serious. None of the 144 serious AEs reported for FS VH S/D was considered related to investigational product by the investigator.
Study 550001

Study Objectives
The objective of this study was to evaluate efficacy in terms of haemostasis as well as safety of FS VH S/D during and after total hip replacement when applied to bleeding bone and soft tissue surfaces as compared to a control group receiving no FS VH S/D.

Efficacy: The primary efficacy endpoint had originally been total measured blood loss (including intra- and post-operative blood loss) in Phase A but was changed in Amendment 3 for both study phases (A and B) to post-operative blood loss determined by recording the amount of blood collected by postoperative drainage.

Study design
Phase II prospective, randomized, controlled, open-label, multi-center, multi-national study with the aim of evaluating efficacy in terms of haemostasis and safety of FS VH S/D in subjects undergoing total hip replacement with cement-free hip prostheses.
Eligible subjects were randomised to receive FS VH S/D in addition to standard haemostatic treatment or to the control group which received standard haemostatic treatment alone. Originally this trial was planned as a phase III study, and the first part, phase A was conducted in 58 patients, that showed that there was no difference in blood loss between the treatment arm and the control arm.

The study design was amended, and a phase B was started which introduced changes to the design that included an increase in the amount of FS VH S/D to be used, from 2.0 – 4.0mL of FS VH S/D in Phase A of the study, to a dose range from 7.0 – 10.0mL in Phase B.

Other changes included the location and mode of application of FS VH S/D which entailed application of the total amount of the study product at the end of the intervention; a shifting of randomization from prior to surgery to the end of the intervention to minimize bias; and a change in the primary endpoint from total measured blood loss (including intra- and post-operative blood loss) to post-operative blood loss, because intra-operative blood loss was hardly affected due to the administration of FS VH S/D at the end of the surgical procedure.

The status of the blinding was changed from single blind to open label as some of the patients were conscious during surgery due to the use of spinal and epidural anaesthesia, which meant that blinding was not an option.

As a consequence of these changes the study was downgraded from a phase III to a phase II exploratory study which was to include a total of 99 subjects instead of the originally planned 150. A total of 42 subjects were randomized in a ratio of 2:1 to either the FS VH S/D or the control group in Phase B. The study product was applied as a single treatment intra-operatively.

Results

Efficacy analysis

Disposition of Subjects

A total of 67 subjects were enrolled in Phase A of the study. Of these, six subjects were not randomized. The remaining 61 subjects were randomized but three of these did not undergo the intended surgery. Of the 58 subjects undergoing surgery as defined in the study protocol, 26 were randomized to receive standard haemostatic treatment and FS VH S/D and 32 to receive standard haemostatic treatment alone. A total of 44 subjects were enrolled in Phase B of the study. Of these, 42 were randomized, 26 to the FS VH S/D group and 16 to the control group.

The sponsor has stated that as study 550001 is an exploratory study, the efficacy results are not pivotal to support the claim of efficacy of FS VH S/D in terms of haemostasis as the sample size in this study was, too small to draw any final conclusions as to the efficacy of FS VH S/D in reducing blood loss after total hip replacement using cement-free prostheses. Nevertheless they are briefly presented below for the ITT population.
Table showing blood loss in both treatment arms for study 550001

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Std dev</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra Op</td>
<td>Control</td>
<td>32</td>
<td>752.1</td>
<td>678.5</td>
<td>385.8</td>
<td>0.2806</td>
</tr>
<tr>
<td></td>
<td>FS VH S/D</td>
<td>26</td>
<td>873.8</td>
<td>811.0</td>
<td>507.4</td>
<td></td>
</tr>
<tr>
<td>Post Op</td>
<td>Control</td>
<td>32</td>
<td>802.8</td>
<td>747.5</td>
<td>404.0</td>
<td>0.8328</td>
</tr>
<tr>
<td></td>
<td>FS VH S/D</td>
<td>26</td>
<td>832.7</td>
<td>790.0</td>
<td>399.4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Control</td>
<td>32</td>
<td>1554.9</td>
<td>1617.0</td>
<td>527.0</td>
<td>0.8025</td>
</tr>
<tr>
<td></td>
<td>FS VH S/D</td>
<td>26</td>
<td>1697.2</td>
<td>1428.5</td>
<td>773.3</td>
<td></td>
</tr>
<tr>
<td><strong>Phase B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra Op</td>
<td>Control</td>
<td>16</td>
<td>515.1</td>
<td>464.0</td>
<td>221.1</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td>FS VH S/D</td>
<td>26</td>
<td>819.2</td>
<td>804.5</td>
<td>298.8</td>
<td></td>
</tr>
<tr>
<td>Post Op</td>
<td>Control</td>
<td>16</td>
<td>772.6</td>
<td>760.5</td>
<td>302.0</td>
<td>0.8459</td>
</tr>
<tr>
<td></td>
<td>FS VH S/D</td>
<td>26</td>
<td>836.7</td>
<td>810.0</td>
<td>424.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Control</td>
<td>16</td>
<td>1287.7</td>
<td>1176.5</td>
<td>415.7</td>
<td>0.0420</td>
</tr>
<tr>
<td></td>
<td>FS VH S/D</td>
<td>26</td>
<td>1655.9</td>
<td>1674.5</td>
<td>633.5</td>
<td></td>
</tr>
</tbody>
</table>

Due to major differences in the design of Phases A and B, data obtained were not comparable between the two phases and therefore each was analyzed separately.

The study only had exploratory aspects. Therefore, analysis of efficacy entailed data exploration, but tests of hypotheses were also carried out. However, the results of these tests were to be interpreted in a descriptive way.

**Safety analysis**

Safety was assessed in 57 subjects who participated in Phase A and in 42 subjects who participated in Phase B of the study. In Phase A, the volume of study product applied to the 31 subjects in the FS VH S/D group ranged between 2.0mL and 4.0mL. In Phase B, the 27 subjects in the FS VH S/D group received doses between 7.0 mL and 10.0 mL of the study product.

In both phases of the study all participating subjects reported AEs. The sponsor has stated that none of the AEs reported were considered by the investigator to be related to the use of the study drug in either of the study phases.

The majority of the AEs reported in both phases and in both treatment groups were of mild or moderate severity.

During Phase A only three, and during Phase B only two subjects reported SAEs which were all unrelated to the used of the study drug. No deaths occurred during the study.

As was to be expected after major surgery, the analysis of AEs by preferred term and system organ class showed that post-procedural pain, post-operative anaemia (system organ class of injury, poisoning, and procedural complications), sleep disorders (system organ class of psychiatric disorders) and post-operative nausea (system organ class of gastrointestinal disorders) were the symptoms most frequently reported in both the FS VH S/D group and the control group during both phases.
A comparison of the AEs which occurred in ≥5% of the subjects in any group showed that the number of subjects with specific symptoms was similar in the FS VH S/D and the control group in either study phase.

Table showing overview of adverse events

<table>
<thead>
<tr>
<th>FS VH S/D – Control, Phase A, SAF Data Set (Study 550001)</th>
<th>n</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number of subjects with AEs</td>
<td>31</td>
<td>31</td>
<td>100.0</td>
</tr>
<tr>
<td>1. Number of subjects with AEs</td>
<td>26</td>
<td>26</td>
<td>100.0</td>
</tr>
<tr>
<td>2. Number of subjects with unrelated AEs</td>
<td>31</td>
<td>31</td>
<td>100.0</td>
</tr>
<tr>
<td>2. Number of subjects with unrelated AEs</td>
<td>26</td>
<td>26</td>
<td>100.0</td>
</tr>
<tr>
<td>5. Number of subjects with mild AEs</td>
<td>26</td>
<td>31</td>
<td>83.87</td>
</tr>
<tr>
<td>5. Number of subjects with mild AEs</td>
<td>25</td>
<td>26</td>
<td>96.15</td>
</tr>
<tr>
<td>6. Number of subjects with moderate AEs</td>
<td>21</td>
<td>31</td>
<td>67.74</td>
</tr>
<tr>
<td>6. Number of subjects with moderate AEs</td>
<td>19</td>
<td>26</td>
<td>73.08</td>
</tr>
<tr>
<td>7. Number of subjects with severe AEs</td>
<td>1</td>
<td>31</td>
<td>3.23</td>
</tr>
<tr>
<td>7. Number of subjects with severe AEs</td>
<td>2</td>
<td>26</td>
<td>7.69</td>
</tr>
<tr>
<td>8. Number of subjects with SAEs</td>
<td>1</td>
<td>31</td>
<td>3.23</td>
</tr>
<tr>
<td>8. Number of subjects with SAEs</td>
<td>2</td>
<td>26</td>
<td>7.69</td>
</tr>
</tbody>
</table>

The changes in laboratory parameters (blood count, blood chemistries, and coagulation parameters) from baseline were as expected after major surgery in both study phases and in the FS VH S/D group as well as in the control group. Changes were similar in their extent in both treatment groups. The vast majority of all out-of-range laboratory results which were considered to be clinically significant by the investigators were attributable to the surgery performed. In very few instances underlying conditions other than surgery were identified and none of the clinically significant out-of-range laboratory values was attributed to the use of the study product.

In both study phases and in the FS VH S/D group as well as in the control group, a slight increase in body temperature and in heart rate could be observed while systolic and diastolic blood pressure slightly decreased. Changes in vital signs over baseline were similar in their extent in both the FS VH S/D group and the control group. None of the follow-up ECGs performed in the study were considered to be abnormal and clinically significant.

**Study 550002**

**Study Objectives**

- To evaluate the efficacy of FS VH S/D in terms of reducing lymphatic leakage by sealing of the axillary lymphatics
- To monitor the safety of FS VH S/D
Efficacy measures
Efficacy was assessed in terms of the duration in days of post-operative axillary drainage, secondary efficacy endpoints included: total axillary drainage volume, daily axillary drainage volume, number of treated wound infections at the axillary wound, and number of axillary symptomatic seromas treated by axillary puncture. Safety was assessed in terms of AEs, physical examinations, vital signs and laboratory assessments. Quality of life was to be assessed with a questionnaire.

Design
Randomised, controlled, single-blind, parallel-group, multi-national, multi-centre study investigating the effect of intra-operative application of FS VH S/D in the reduction of the duration of axillary drainage post-operatively compared to conventional surgical methods alone. The Subjects in this study were 161 female patients with breast cancer who were scheduled for level I and II axillary lymph node dissection. Eligible subjects that met the entry criteria were randomised into two groups, with 79 patients receiving treatment with FS VH SD in addition to standard surgical treatment.

Apart from the use of FS VH SD, the surgical procedures were the same for both groups of patients. In this study it was only possible to blind the patient as it was not possible to blind the investigator. Therefore patients were randomised during surgery to avoid bias on the part of the investigator, as the knowledge of the arm the patient has been randomised to could influence the surgeon in the way the surgical procedure is carried out with due diligence with securing haemostasis during surgery in the control arm on conventional treatment only.

For the FS VH S/D treatment arm, up to 4 mL of FS VH S/D was applied topically. The primary efficacy endpoint was the duration of post-operative axillary drainage (in days) which was analysed using the Wilcoxon-Mann-Whitney test. During the course of the study, the protocol was amended three times prior to study start as well as during the study in order to change the patient selection and also to introduce minor changes to the study procedures.

Results

Efficacy analysis

Diagram showing patient disposition in the study

<table>
<thead>
<tr>
<th>Surgery Performed: 161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized: 161</td>
</tr>
<tr>
<td>FS VH S/D: 79</td>
</tr>
<tr>
<td>Completed study: 77</td>
</tr>
<tr>
<td>Withdrawn: 2</td>
</tr>
<tr>
<td>CONTROL: 82</td>
</tr>
<tr>
<td>Completed study: 80</td>
</tr>
<tr>
<td>Withdrawn: 2</td>
</tr>
</tbody>
</table>

41
The primary efficacy endpoint is the post-operative axillary drainage in days. The axillary drain is to be removed when the daily volume was less than or equal to 30mL per 24 hours.

The ITT analysis data set (full analysis set) and the PP analysis data set (efficacy subset) were analyzed. The ITT analysis data set comprised all subjects randomized who underwent surgery, regardless of whether or not they received the correct treatment according to the randomization scheme. All eligible subjects who received standard treatment and FS VH S/D or standard treatment alone and had all required study evaluations related to the endpoint were included in the PP analysis data set.

Data set analysed for study 550002

<table>
<thead>
<tr>
<th>Data Set Analyzed</th>
<th>All Subjects</th>
<th>FS VH S/D</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subjects entered (Surgery performed and subjects randomized)</td>
<td>161</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>2. Intent-to-treat population (Same population as subjects entered)</td>
<td>161</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>3. Per-protocol population</td>
<td>155</td>
<td>76</td>
<td>79</td>
</tr>
<tr>
<td>4. Safety population</td>
<td>161</td>
<td>79</td>
<td>82</td>
</tr>
</tbody>
</table>

The following table presents details of the analysis of the primary endpoint, the duration (in days) of post-operative axillary drainage for the ITT population.

<table>
<thead>
<tr>
<th>Treatment ITT data</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Standard Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>82</td>
<td>6.1</td>
<td>6.0</td>
<td>3.0</td>
<td>0.0821</td>
</tr>
<tr>
<td>FS VH S/D</td>
<td>79</td>
<td>7.0</td>
<td>7.0</td>
<td>3.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment PP data</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Standard deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>58</td>
<td>6.1</td>
<td>6.0</td>
<td>2.8</td>
<td>0.3166</td>
</tr>
<tr>
<td>FS VH S/D</td>
<td>62</td>
<td>6.6</td>
<td>6.0</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

The difference between the treatment groups did not achieve statistical significance although the estimated difference was approximately one day which had been specified in the protocol as being clinically relevant. However as for study 550001 it should be noted that the difference is in favour of the control group and not the fibrin sealant. For the PP population a median duration of 6.0 days was seen for both treatments.

Safety Analysis

Table showing number of subjects with adverse events.

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Treatment Group</th>
<th>n</th>
<th>N</th>
<th>percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subject with AE</td>
<td>Control</td>
<td>73</td>
<td>82</td>
<td>89.2</td>
</tr>
<tr>
<td>No. of subjects with AE</td>
<td>FS VH S/D</td>
<td>75</td>
<td>79</td>
<td>94.94</td>
</tr>
</tbody>
</table>
Safety was assessed in terms of adverse events (AE), physical examination, vital signs and laboratory investigations. All subjects undergoing surgery and receiving FS VH S/D or conventional treatment only were to be included in the safety analysis and evaluated according to the actual treatment received. No deaths occurred during this study. A total of 16 SAEs were reported in 14 subjects, 4 SAEs in 4/79 subjects (5.06%) in the FS VH S/D group and 12 SAEs in 10/82 subjects (12.2%) in the control group. All SAEs reported in both study groups were judged by the investigators as being unrelated to the use of FS VH S/D or reference therapy (conventional surgical treatment), respectively.

The most frequently reported SAE in both study groups was the repeat of the surgical procedure due to incomplete resection of the tumor. In the FS VH S/D group, 75 of 79 subjects reported AEs. A total of 209 non-serious AEs were reported in the FS VH S/D group. The majority of AEs were mild (148/209) and moderate (58/209), with 3/209 severe cases reported. In the control group, 73/82 subjects reported AEs. A total of 194 AEs occurred: 149/194 were mild, 45/194 were moderate, and none were severe.

### Table showing adverse events observed and rate

<table>
<thead>
<tr>
<th>SOC</th>
<th>Treatment group</th>
<th>Relationship</th>
<th>Severity</th>
<th>n</th>
<th>N</th>
<th>Freq uency %</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>CONTROL</td>
<td>POSSIBLE</td>
<td>1-MILD</td>
<td>11</td>
<td>11</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>TOTAL</td>
<td>CONTROL</td>
<td>UNRELATED</td>
<td>1-MILD</td>
<td>138</td>
<td>195</td>
<td>70.8</td>
<td>70.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>CONTROL</td>
<td>UNRELATED</td>
<td>2-MODERATE</td>
<td>45</td>
<td>195</td>
<td>23.1</td>
<td>23.1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>CONTROL</td>
<td>UNRELATED</td>
<td>4-SERIOUS</td>
<td>12</td>
<td>195</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>POSSIBLE</td>
<td>1-MILD</td>
<td>17</td>
<td>28</td>
<td>60.7</td>
<td>60.7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>PROBABLE</td>
<td>1-MILD</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>UNRELATED</td>
<td>1-MILD</td>
<td>129</td>
<td>183</td>
<td>70.5</td>
<td>70.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>UNRELATED</td>
<td>2-MODERATE</td>
<td>47</td>
<td>183</td>
<td>25.7</td>
<td>25.7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>POSSIBLE</td>
<td>2-MODERATE</td>
<td>11</td>
<td>28</td>
<td>39.3</td>
<td>39.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>UNRELATED</td>
<td>3-SEVERE</td>
<td>3</td>
<td>183</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>FS VH S/D</td>
<td>UNRELATED</td>
<td>4-SERIOUS</td>
<td>4</td>
<td>183</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**EXPERT REPORT**
The clinical expert report was written by a suitably qualified person and is satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS**
This is satisfactory.

**DISCUSSION**
The studies conducted were to show that the new second dedicated virus inactivation step, S/D treatment, does not alter the structure and function of the main active molecules of the product, fibrinogen and thrombin.
The pivotal study conducted to meet the regulatory requirements is study 550003, which has provided the primary evidence to support the efficacy of the new formulation. Safety and efficacy have been justified and the risk/benefit profile of this product is satisfactory.

**CONCLUSIONS**
There is adequate documentation and sufficient justification for efficacy and safety for the proposed indications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of TISSEEL Ready to use are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No toxicity was demonstrated, and no new toxicological problems for these products were found. The studies demonstrated the bioequivalence of TISSEEL VH S/D (frozen and lyophilized) to the licensed product TISSEEL VH.

EFFICACY
The clinical studies performed have shown that the new second dedicated virus inactivation step, S/D treatment, does not alter the structure and function of the main active molecules of the product, fibrinogen and thrombin. Therefore, they have demonstrated that the product is an effective and safe tissue sealant indicated for supportive treatment, where standard surgical techniques are insufficient, for:
- The improvement of haemostasis
- As a tissue glue to promote adhesion/sealing or as suture support:
  - in gastrointestinal anastomoses
  - in neurosurgery where contact with cerebro-spinal fluid or dura mater can occur.

No significant new or unexpected safety concerns were found during the clinical development.

The summary of product characteristics, patient information leaflet and labelling are appropriate for a product of this type.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant clinical safety concerns were identified, and some benefit has been shown to be associated with TISSEEL Ready to use. The risk benefit is therefore considered to be positive.
TISSEEL Ready to use

(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on the 18\textsuperscript{th} February 2007.
2 Following standard checks the MHRA informed the applicant that its application was considered valid on the 9\textsuperscript{th} of March 2007.
3 Following assessment of the submitted data, a request for supplementary information relating to the pharmaceutical dossier was sent to the applicant on the 3\textsuperscript{rd} of August 2007.
4 The applicant submitted its response to the supplementary information request in a letter dated 12\textsuperscript{th} of October 2007, and again on the 6\textsuperscript{th} of December 2007 and the 8\textsuperscript{th} of January 2008.
5 Following further assessment of the application, the MHRA requested further information relating to the clinical dossier on the 5\textsuperscript{th} of December 2007.
6 The applicant responded, providing further information, on the 13\textsuperscript{th} of February 2008.
7 The applicant submitted results of a further study as per its commitment to the Pharmaceutical Assessor on the 29\textsuperscript{th} of June 2008.
8 The application was determined on the 3\textsuperscript{rd} of October 2008.
TISSEEL Ready to use
(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
TISSEEL Ready to use
Solutions for Sealant ▼

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Component 1:
Sealer Protein Solution

Human Fibrinogen (Clottable Protein) 91 mg^{(1)}/ml
Aprotinin 3000 KIU^{(2)}/ml

Component 2:
Thrombin Solution

Human Thrombin 500 IU^{(3)}/ml
Calcium Chloride 40 µmol/ml

1 Contained in a total protein concentration of 110.5 mg/ml
2 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)
3 Thrombin activity is calculated using the current WHO International Standard for Thrombin.

For excipients, see section 6.1.

1 prefilled double chamber syringe which contains Sealer Protein Solution (with Aprotinin), deep frozen 1 ml, 2 ml, or 5 ml, in one chamber and Thrombin Solution (with Calcium Chloride), deep frozen 1 ml, 2 ml, or 5 ml, in the other chamber results in 2 ml, 4 ml, or 10 ml total volume of product ready for use.

3 PHARMACEUTICAL FORM
Solutions for Sealant

Colourless to pale yellow and clear to slightly turbid solutions.
4  CLINICAL PARTICULARS

4.1  Therapeutic indications
Supportive treatment where standard surgical techniques are insufficient

- for improvement of hemostasis (see section 5.1)

- as a tissue glue to promote adhesion/sealing, or as suture support:
  - in gastrointestinal anastomoses
  - in neurosurgery where contact with cerebro-spinal fluid or dura mater may occur

4.2  Posology and method of administration
The use of TISSEEL Ready to use is restricted to experienced physicians.

Posology:

The amount of TISSEEL Ready to use to be applied and the frequency of application should always be oriented towards the underlying clinical needs of 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.

To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the mixed Sealer Protein - Thrombin Solutions, or of the individual components, should be applied.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 4 to 20 ml. For some procedures, larger volumes may be required.

The initial amount 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.
As a guideline for the gluing of surfaces, 1 pack of TISSEEL Ready to use 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm².

When TISSEEL Ready to use is applied by spray application, the same quantity will be sufficient to coat considerably larger areas, depending on the specific indication and the individual case.

**Method and route of administration**

For epilesional use.

Solution preparation, see section 6.6.

Before application, the surface of the wound should be as dry as possible.

For detailed instructions, see section 6.6.

### 4.3 Contraindications

TISSEEL Ready to use must not be applied intravascularly.

Hypersensitivity to the active substances or to any of the excipients

TISSEEL Ready to use alone is not indicated for the treatment of active or spurting arterial or venous bleeding which is not controlled by conventional surgical techniques.

### 4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly. Soft tissue injection of TISSEEL Ready to use carries the risk of an anaphylactoid reaction and / or local tissue damage.

TISSEEL Ready to use should only be applied as a thin layer. Excessive clot thickness may negatively interfere with the product’s efficacy and the wound healing process.

In two retrospective, non-randomized studies in Coronary Artery Bypass Graft (CABG) surgery, patients that received fibrin sealant showed a statistically significant increased risk of mortality. While these studies could not provide a determination of a causal relationship the increased risk associated with the use of TISSEEL Ready to use in these patients cannot be excluded. Therefore, additional care should be taken to avoid inadvertent intravascular administration of this product.
Injection of Sealer Protein and/or Thrombin Solution carries a risk of anaphylactoid reactions. Intravascular and intraventricular administration carries the additional risk of a thromboembolic complication. Both complications may be life-threatening. Therefore, care should be taken to ensure that Sealer Protein and/or Thrombin Solution are only applied topically.

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

TISSEEL Ready to use contains bovine protein (aprotinin). Even in the case of strict local application there is a risk of anaphylactic reaction, linked to the presence of bovine aprotinin. The risk seems higher in case of previous exposure even if it was well tolerated. Therefore, any use of aprotinin, or aprotinin-containing products, should be recorded in the patients’ records.

In case of shock, standard medical treatment for shock should be implemented.

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

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

The measures taken may be of limited value against small non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anemia).

It is strongly recommended that every time a patient receives a dose of TISSEEL Ready to use, the name and batch number of the product are recorded in order to maintain a record of the batches used.

Adequate data are not available to support the use of this product in application through a flexible endoscope for treatment of bleeding or in vascular surgery.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.


4.6 Pregnancy and lactation

The safety of fibrin sealants for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and peri-and postnatal development.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants / haemostatics.

In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin (see Section 4.4) or any other constituents of the product.

Even if a second treatment with TISSEEL Ready to use was well tolerated, a subsequent administration of TISSEEL or systemic administration of aprotinin may result in severe anaphylactic reactions.

In the event of hypersensitivity reactions, administration is to be discontinued and state-of-the-art emergency measures are to be taken.

Soft tissue injection of TISSEEL Ready to use carries the risk of an anaphylactoid reaction and / or local tissue damage (see Section 4.4).

Reactions to antibodies against components of fibrin sealant / haemostatic products may occur rarely.

Inadvertent intravascular injection could lead to thromboembolic events and disseminated intravascular coagulation, and there is also a risk of anaphylactic reaction (see Section 4.4).

For safety with respect to transmissible agents, see Section 4.4.

The undesirable effects reported in the listing hereafter are based on post-market experience for this type of product. Their frequency has been evaluated by using the following criteria: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000).

The undesirable effects listed below reflect the type of undesirable effects that have been reported with TISSEEL Ready to use.

Their incidence rate is <1/10,000, i.e. very rare.
Cardiac disorders
  - Bradycardia, Tachycardia

Gastrointestinal disorders
  - Nausea

General disorders and administration site disorders
  - Hypersensitivity reactions

Immune system disorders
  - Anaphylactic reactions, Allergic reactions, Anaphylactic shock, Urticaria

Injury, poisoning and procedural complications
  - Anaphylactoid reactions

Investigations
  - Drop in blood pressure

Respiratory, thoracic and mediastenal disorders
  - Dyspnoea

Skin and subcutaneous tissue disorders
  - Pruritus

Vascular disorders
  - Flush, (severe) Hypotension, Thromboembolic complication

4.9 Overdose
No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: local hemostatics, ATC code: B02BC; tissue adhesives, ATC code: V03A K
The fibrin adhesion system imitates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is generated from factor XIII by the concerted action of thrombin and calcium ions, stabilizes the clot by the cross-linking of fibrin fibres.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by anti-fibrinolytics. Aprotinin is present in TISSEEL Ready to use as an antifibrinolytic to prevent premature degradation of the clot.

Efficacy in haemostasis has been demonstrated in cardiopulmonary surgery, splenic surgery and neurosurgery.

Use as tissue glue to promote adhesion/sealing or as suture support: Efficacy has been demonstrated in surgeries including gastrointestinal anastomoses and neurosurgical procedures where contact with cerebro-spinal fluid or dura mater can occur.

Clinical studies demonstrating haemostasis, sealing, and tissue adhesion were conducted in at least 4,706 patients. These studies were performed in a multitude of surgical specialties, surgical procedures and applications techniques, including but not limited to haemostasis (n=1300), gastrointestinal anastomoses (n=1,114), neurosurgery (n=511). There is limited experience in children during cardiac surgery (age 4-134 months: n=14).

Fibrin Sealant VH S/D (frozen presentation) was evaluated in a prospective, parallel design, randomized (1:1), double-blind, multicenter clinical study against a previous single virus inactivated formulation of the product, Fibrin Sealant VH (lyophilized presentation), in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) and median sternotomy. Patients were treated with Fibrin Sealant VH S/D or the control product only when hemostasis was not achieved by conventional surgical methods. For the endpoint, hemostasis achieved at the primary treatment site within 5 minutes of treatment and maintained until closure of the surgical wound, Fibrin Sealant VH S/D was non-inferior to the earlier formulation of the product using a one-sided 97.5% confidence interval on the difference in the proportion of subjects successfully treated.

<table>
<thead>
<tr>
<th>Hemostasis within 5 minutes and maintained until surgical closure</th>
<th>FIBRIN SEALANT VH S/D</th>
<th>FIBRIN SEALANT VH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat Analysis</td>
<td>127/144 (88.2%)</td>
<td>129/144 (89.6%)</td>
</tr>
<tr>
<td>Per Protocol Analysis</td>
<td>108/123 (87.8%)</td>
<td>122/135 (90.4%)</td>
</tr>
</tbody>
</table>

No difference to control groups not receiving Fibrin Sealant VH S/D was observed in an exploratory study in hip joint replacement for postoperative blood loss and in a study in axillary lymph node dissection for duration of axillary drainage.

5.2 Pharmacokinetic properties

Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Fibrin sealants/hemostatics are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis.
5.3 Preclinical Safety Data

No preclinical safety data are available for Fibrin Sealant VH S/D on subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity or immune stimulation.
Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of Fibrin Sealant VH S/D (frozen presentation). There was no evidence of mutagenicity in appropriate in vitro tests.
Fibrin Sealant VH S/D (frozen presentation) was well tolerated in wound healing models in rats and rabbits.
The Sealer Protein Solutions of Fibrin Sealant VH S/D (frozen and lyophilized presentations) were also well tolerated by in vitro human fibroblast cultures demonstrating cellular compatibility and non-cytotoxicity.
Based on a detailed literature review, toxicity of the residual solvent/detergent reagents (see 6.1) on Fibrin Sealant VH S/D can be essentially excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Component 1: Sealer Protein Solution
Human Albumin
L-Histidine
Niacinamide
Polysorbate 80 (Tween 80)
Sodium Citrate Dihydrate
Water for Injections

Component 2: Thrombin Solution
Human Albumin
Sodium Chloride
Water for Injections

6.2 Incompatibilities
Compatibility with other medicinal products has not been examined.

6.3 Shelf life
TISSEEL Ready to use has a shelf life of two years. The expiry date is stated on the package.
Shelf life for thawed product see section 6.6.
6.4 Special precautions for storage
Keep out of the reach and sight of children.
Store in a freezer (at \( \leq 18^\circ\text{C} \)). The cold storage chain must not be interrupted until use.
Keep TISSEEL Ready to use in the outer carton to protect from light.
Use the thawed solutions within 72 hours. Do not refreeze or refrigerate after thawing.

6.5 Nature and contents of container
Both Sealer Protein Solution and Thrombin Solution are contained in a single-use double-chamber syringe made of polypropylene.

Each pack of TISSEEL Ready to use contains:

- One single-use double-chamber syringe with Sealer Protein Solution 1 ml, 2 ml, or 5 ml, deep-frozen, in one chamber; and Thrombin Solution 1 ml, 2 ml, or 5 ml, deep frozen, in the other chamber.
  1) One chamber contains: Component 1 - Sealer Protein Solution
     Active substances: Human Fibrinogen (Clottable Protein) 72 – 110 mg/ml, Human Factor XIII \( \leq 10 \text{ U/ml} \), Aprotinin (bovine) 3000 KIU/ml
  2) One chamber contains: Component 2 - Thrombin Solution
     Active substances: Human Thrombin 500 IU/ml, Calcium Chloride 40 \( \mu \text{mol/ml} \)

- One set of application devices (DUO - Set: 2 joining pieces, 4 application needles (blunt), 1 Double syringe plunger)

TISSEEL Ready to use is available in the following pack sizes:

- TISSEEL Ready to use 2 ml (containing 1 ml of Sealer Protein Solution and 1 ml of Thrombin Solution)
- TISSEEL Ready to use 4 ml (containing 2 ml of Sealer Protein Solution and 2 ml of Thrombin Solution)
- TISSEEL Ready to use 10 ml (containing 5 ml of Sealer Protein Solution and 5 ml of Thrombin Solution)

Not all pack sizes may be marketed.
Other accessories for application of the product can be obtained from BAXTER.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
General
Before administration of TISSEEL Ready to use care has to be taken that parts of the body outside the desired application area are sufficiently covered to prevent tissue adhesion at undesired sites.
To prevent TISSEEL Ready to use from adhering to gloves and instruments, wet these with sodium chloride solution before contact.
Handling and Preparation
Both the Sealer Protein Solution and the Thrombin Solution are contained in a single-use double-chamber syringe. The nozzles of the pre-filled double-chamber syringe are closed by one tip cap and each barrel of the syringe is closed by a silicone rubber stopper. The entire assembly is packed and hermetically sealed in two sterilized aluminum-plastic-compound bags under aseptic conditions. The inner bag and its contents are sterile unless the integrity of the outside package is compromised.

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. (In order to control the specified temperature range, the water temperature should be monitored using a thermometer and the water should be changed as necessary. When using a sterile water bath for thawing and warming, the pre-filled double chamber syringe assembly should be removed from the aluminum-plastic bags.)

The protective syringe cap should not be removed until thawing is complete and application tip is ready to be attached. Do not use TISSEEL Ready to use unless it is completely thawed and warmed.

Thaw pre-filled syringes in one of the three following options:

The thawing and warming times when using a sterile water bath are indicated in Table 1 below.

Table 1: Thawing and Warming Times with Sterile Water Bath at 33°C to a maximum of 37°C

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Thawing and Warming Times (Product Removed from aluminum-plastic bags)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
<td>5 minutes</td>
</tr>
<tr>
<td>4 ml</td>
<td>5 minutes</td>
</tr>
<tr>
<td>10 ml</td>
<td>12 minutes</td>
</tr>
</tbody>
</table>

Alternatively, the sealant components may be thawed and warmed in an incubator between 33°C and 37°C. The thawing and warming times in the incubator are indicated in Table 2 below. The times refer to product in the aluminum-plastic bags.

Table 2: Thawing and Warming Times in Incubator at 33°C to a maximum of 37°C

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Thawing and Warming Times in Incubator (product in aluminum-plastic bags)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
<td>40 minutes</td>
</tr>
<tr>
<td>4 ml</td>
<td>85 minutes</td>
</tr>
<tr>
<td>10 ml</td>
<td>105 minutes</td>
</tr>
</tbody>
</table>

A third alternative is to thaw the product at room temperature. Times given in Table 3 are minimum times for thawing at room temperature. The maximum time the product can be kept (in both aluminum-plastic bags) at room temperature is 72 hours.
When thawing at room temperature, the product must be additionally warmed to 33°C – 37°C in an incubator just before use. Respective thawing times in the incubator are also given in Table 3.

Table 3. Thawing and warming times at Room Temperature (=RT) followed by an additional warming, prior to use, in Incubator at 33°C to a maximum of 37°C

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Thawing Times at Room Temperature (product in aluminum-plastic bags)</th>
<th>Warming Times at 33-37°C in Incubator after Thawing at RT (product in aluminum-plastic bags)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
<td>60 minutes</td>
<td>+ 15 minutes</td>
</tr>
<tr>
<td>4 ml</td>
<td>110 minutes</td>
<td>+ 25 minutes</td>
</tr>
<tr>
<td>10 ml</td>
<td>160 minutes</td>
<td>+ 35 minutes</td>
</tr>
</tbody>
</table>

**Note:** Do not thaw by holding product in your hands.  
Do not microwave.  
After thawing do not refrigerate or refreeze.

To facilitate optimal blending of the two solutions, the two sealant components must be warmed to 33 – 37°C immediately before use. (The temperature of 37°C must, however, not be exceeded!)

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration.

The thawed Sealer Protein Solution should be a slightly viscous liquid. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (e.g., due to an interruption of the cold storage chain or by overheating during warming). In this case, the TISSEEL Ready to use must not be used.

Thawed, unopened pouches may be stored for up to 72 hours at controlled room temperature (not exceeding +25°C) after removal from the freezer. If not used within 72 hours after thawing, TISSEEL Ready to use has to be discarded.

Once thawed, TISSEEL Ready to use must not be refrozen or refrigerated (the sealer protein component forms a gel at refrigerator temperature).

For further preparation instructions please refer to the responsible nurse or medical doctor.

**ADMINISTRATION**

For application, the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution has to be connected to a joining piece and an application needle as provided in the accompanying set of devices. The common plunger of the double-chamber syringe ensures that equal volumes are fed through the joining piece before being mixed in the application needle and ejected.
- Connect the nozzles of the double-chamber syringe to the joining piece ensuring that they are firmly fixed. Secure the joining piece by fastening the tether strap to the double-chamber syringe. If the pull strap tears, use the spare joining piece. If none is available, further use is still possible but tightness of the connection needs to be ensured to prevent any risk of leaking.

- Fit an application needle onto the joining piece.

- Do not expel the air remaining inside the joining piece or application needle until you start actual application as the aperture of the needle may clog otherwise.

- Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

If application of the fibrin sealant components is interrupted, clogging occurs immediately in the needle. Replace the application needle with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

**Note:** After blending of the sealant components, the fibrin sealant starts to set within seconds on account of the high Thrombin concentration (500 IU/ml).

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g. endoscopic use, minimally invasive surgery, application to large or difficult-to-access areas. When using these application devices, strictly follow the Instructions for Use of the devices.
After the two components have been applied, approximate the wound areas. Fix or hold the glued parts with continuous gentle pressure in the desired position for about 3–5 minutes to ensure that the setting fibrin sealant adheres firmly to the surrounding tissue.

In certain applications, biocompatible material, such as collagen fleece, is used as a carrier substance or for reinforcement.

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

7 **MARKETING AUTHORISATION HOLDER**
Baxter Healthcare Limited
Caxton Way
Thetford
Norfolk
IP24 3SE
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00116/0627

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**
03/10/2008

10 **DATE OF REVISION OF THE TEXT**
03/10/2008
TISSEEL Ready to use

(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627
Please read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What TISSEEL is and what it is used for
2. Before you use TISSEEL
3. How to use TISSEEL
4. Possible side effects
5. How to store TISSEEL
6. Further information

1. WHAT TISSEEL IS AND WHAT IT IS USED FOR

What TISSEEL is
The name of your medicine is TISSEEL Ready to use.
Throughout this leaflet TISSEEL Ready to use will be called TISSEEL.
TISSEEL is a two-component tissue sealant, and it contains two of the proteins that make blood clot. These proteins are called fibrinogen and thrombin. When these proteins mix during application, they form a clot where the surgeon applies them.
TISSEEL is prepared as two solutions (Sealer Protein Solution and Thrombin Solution), which mix when applied.

What TISSEEL is used for
TISSEEL is a fibrin or tissue sealant. During surgery, tissues may bleed and it may not be possible for the surgeon to control this bleeding using stitches, or by applying pressure. TISSEEL is applied to the surface of tissues, either to control bleeding, or to stop (or prevent) leaks of other types of fluid, by creating a watertight seal.
TISSEEL can be used even if your blood does not clot properly, e.g. when you are being treated with heparin against thrombosis. It is also used as a tissue glue to achieve a adhesion/sealing or as a suture support in surgery.
The clot produced by TISSEEL is very similar to a natural blood clot and this means that it will dissolve naturally and leave no residue. However, bovine aprotinin is added to increase the longevity of the clot and to prevent its premature dissolution.

2. BEFORE YOU USE TISSEEL

Do not use TISSEEL in the following situations:
- TISSEEL must not be used for massive or brisk bleeding.
- TISSEEL MUST NOT be injected into blood vessels (veins or arteries), or into tissues. As TISSEEL forms a clot where it is applied, injecting TISSEEL may cause serious reactions. TISSEEL should only be applied to the surface of tissues at a thin layer where it is needed. If you are going to have a coronary bypass surgery, special care needs to be taken to avoid injecting TISSEEL into blood vessels.
- If you are allergic (hypersensitive) to bovine proteins or any of the other ingredients of TISSEEL must not be used.

TISSEEL contains a bovine protein, called aprotinin. Even when this protein is applied in small areas, there is a risk of a reaction known as anaphylaxis, or a severe allergic (hypersensitive) reaction.

Take special care with TISSEEL
- If you have ever received TISSEEL or aprotinin before, your body may have become sensitive to it. It is possible you may be allergic to this material, even if there were no reaction to the first application. If you think you have received either product in a previous operation, you have to inform your doctor about this.
- If the surgeon or operating team sees any sign of an allergic reaction during the application of TISSEEL, they will stop using TISSEEL immediately and will take the adequate measures.

Using other medicines
There are no known interactions between TISSEEL and other medicinal products. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking TISSEEL with food and drink
Please ask your doctor. The doctor will decide if you are allowed to eat and drink before the application of TISSEEL.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicines. Please inform your doctor before using TISSEEL if you are or could be pregnant or if you are breast-feeding. Your doctor will decide if you can use TISSEEL during pregnancy or breast-feeding.

Driving and using machines
TISSEEL will not affect your ability to drive or operate other types of machines.
Important Information about the potential risk of infection from donor human plasma

When medicines are made from human blood or plasma, certain steps are taken to prevent infections being passed on to patients. Blood and plasma donors are carefully selected to make sure that those at risk of carrying infections are excluded. In addition, each donation and plasma pool is tested for signs of viruses or 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.

3. HOW TO USE TISSEEK
   • TISSEEK is only applied during a surgical operation, and it is applied by the surgeon.
   • The amount of TISSEEK that will be used depends on a number of factors, including the type of surgery, the surface area of tissue to be treated during your operation and the way TISSEEK is applied. The surgeon will decide how much is appropriate, and will apply just enough to form a thin, even layer over the tissue. If this does not seem to be enough, a second layer can be applied.
   • During your operation, the surgeon will apply TISSEEK onto the relevant tissue surface, using the special application device provided. This device ensures that equal amounts of both components are applied at the same time – which is important for the optimal effect of TISSEEK.

If you take more TISSEEK than you should
   TISSEEK is only applied during a surgical operation. It is applied by the surgeon and the amount of TISSEEK is determined by the surgeon.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
   Like all medicines, TISSEEK can cause side effects, although not everybody gets them.
   • There is a slight possibility that you might react allergically to one of the components of TISSEEK. This is more likely if you have been treated with TISSEEK or aprotinin during a previous operation. Allergic reactions can be serious, and it is very important that you discuss this possibility in detail with your doctor.
   • In very rare cases, allergic reactions of the anaphylactic/anaphylactoid type may occur. Early symptoms of allergic reactions can be: flushing, a fall in blood pressure, increased or decreased pulse rate, nausea (feeling sick), itching, difficulty breathing.
   • The surgical team treating you will be aware of the risk of this type of reaction – if they see any symptoms, the application of TISSEEK will be stopped immediately. Severe symptoms may require emergency treatment.
   • If TISSEEK is injected into soft tissues, it can cause local tissue damage.
   • If TISSEEK is injected into blood vessels (veins or arteries), it can cause clotting to form (thrombosis).
   • As TISSEEK is made from plasma from blood donations, the risk of infection cannot be totally excluded, but the manufacturer undertakes numerous measures to reduce the risk (see section 2).
   • There are also individual reports on occurrence of bleeding, blockage of bowel passage, impaired healing, swellings caused by accumulation of fluid in body tissue, fever, and accumulation of lymph and other clear body fluids near the surgical site.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TISSEEK
   • Keep out of the reach and sight of children.
   • Do not use TISSEEK after the expiry date given on the label.
   • Store at 5–15°C (in a freezer). The cold storage chain must not be interrupted until use.
   • Keep TISSEEK in the original package, to protect from light.
   • After thawing, the solution must not be refrozen or refrigerated!

6. FURTHER INFORMATION
   What TISSEEK contains
   TISSEEK contains two components:

   Component 1 = Sealer Protein Solution:
   The active substances contained in 1 ml of the Sealer Protein solution are:
   Human Fibrinogen, 72 – 110 mg/ml; Aprotinin (bovine), 3000 KIU/ml.
   The excipients are Human Albumin, L-Histidine, Nicotinamide, Polysorbate 80, Sodium Citrate Dihydrate and Water for Injections.

   Component 2 = Thrombin Solution:
   The active substances contained in 1 ml of the Thrombin solution are:
   Human Thrombin, 500 IU/ml; Calcium Chloride, 40 µmol/l.
   The excipients are Human Albumin, Sodium Chloride and Water for Injections.

   What TISSEEK looks like and the contents of the pack
   Both components of TISSEEK Sealer Protein Solution and Thrombin Solution are filled in single-use double-chamber syringes made of polypropylene. Both components are colorless or pale yellow.

   Each pack of TISSEEK contains
   • One pre-filled double-chamber syringe with Sealer Protein Solution (with aprotinin), deep-frozen, in one chamber; and Thrombin Solution (with calcium chloride), deep-frozen, in the other chamber.
- One set of sterile accessory devices (Duo Set: 1 syringe plunger, 2 joining pieces and 4 application cannulas).

TISSEEL is available in the following pack sizes:

- TISSEEL 2 ml (containing 1 ml of Sealer Protein Solution and 1 ml of Thrombin Solution)
- TISSEEL 4 ml (containing 2 ml of Sealer Protein Solution and 2 ml of Thrombin Solution)
- TISSEEL 10 ml (containing 5 ml of Sealer Protein Solution and 5 ml of Thrombin Solution)

TISSEEL is available in pack sizes of 2 ml, 4 ml and 10 ml.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Baxter Healthcare, Caxton Way, Thetford, Norfolk, UK, IP24 3SE

Manufacturer
Baxter AG, Industriestraße 67, A-1221 Vienna, Austria

This leaflet was last approved in: June 2008

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling and disposal

General

Before administering TISSEEL, take care that parts of the body outside the intended application area are adequately covered, so that the medicine does not adhere to tissue at unintended sites.

To prevent TISSEEL from adhering to gloves and instruments, wet these with saline before contact.

Some solutions that contain alcohol, iodine or certain types of metals (these are normally found in disinfectants or antiseptics) may reduce the ability of TISSEEL to work normal. These substances should be removed, as far as possible, before TISSEEL is applied.

It is strongly recommended that every time you receive a dose of TISSEEL, the name and batch number of the product are recorded. This maintains a record of the batches used.

Handling and Preparation

The pre-filled double-chamber syringe is packed and hermetically sealed in two sterilised plastic bags under aseptic conditions. The inner bag and its contents are sterile unless the integrity of the outside package is compromised.

It is recommended to thaw and warm the two sealant components using a sterile water bath at a temperature of 33 – 37°C. The water bath must not exceed a temperature of 37°C. (Check that the temperature is within range by monitoring the water temperature with a thermometer and changing the water as necessary. When using a sterile water bath for thawing and warming, the pre-filled double-chamber syringe should be removed from the aluminium plastic bags.)

The protective syringe cap should not be removed until thawing is complete and application is ready to be attached. Do not use TISSEEL unless it is completely thawed and warmed (liquid consistency).

Thaw pre-filled syringes in one of the three following options:

The thawing and warming times when using a sterile water bath are indicated in Table 1 below:

Table 1: Thawing and Warming Times with Sterile Water Bath at 33°C to a maximum of 37°C

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Thawing and Warming Times (product removed from plastic bags)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
<td>5 minutes</td>
</tr>
<tr>
<td>4 ml</td>
<td>5 minutes</td>
</tr>
<tr>
<td>10 ml</td>
<td>12 minutes</td>
</tr>
</tbody>
</table>

Alternatively, the sealant components may be thawed and warmed in an incubator in between 33°C and 37°C. The thawing and warming times in the incubator are indicated in Table 2 below. The times refer to product in the aluminium plastic bags.

Table 2: Thawing and Warming Times in Incubator at 33°C to a maximum of 37°C

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Thawing and Warming Times in Incubator (product in plastic bags)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
<td>40 minutes</td>
</tr>
<tr>
<td>4 ml</td>
<td>85 minutes</td>
</tr>
<tr>
<td>10 ml</td>
<td>105 minutes</td>
</tr>
</tbody>
</table>

A third alternative is to thaw the product at room temperature. Times given in Table 3 are minimum times for thawing at room temperature. The maximum time the product can be kept (in both plastic bags) at room temperature is 72 hours.

When thawing at room temperature, the product must be additionally warmed to 33°C – 37°C in an incubator shortly before use in order to allow for optimum blending of the two solutions. Respective thawing times in the incubator are also given in Table 3.
Table 3: Thawing and Warming times at Room Temperature (± RT) followed by an additional warming, prior to use, in incubator at 33°C to a maximum of 37°C

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>Thawing Times at Room Temperature (product in plastic bags)</th>
<th>Warming Times at 33 - 37°C in Incubator after thawing at RT (product in plastic bags)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
<td>60 minutes +</td>
<td>15 minutes</td>
</tr>
<tr>
<td>4 ml</td>
<td>110 minutes +</td>
<td>25 minutes</td>
</tr>
<tr>
<td>10 ml</td>
<td>160 minutes +</td>
<td>35 minutes</td>
</tr>
</tbody>
</table>

Note: Do not thaw by holding product in your hands. Do not microwave. After thawing do not refrigerate or refreeze.

To facilitate blending of the two solutions and allow for optimum solidification of the blend, the two sealant components must be warmed to 33 - 37°C. (The temperature of 37°C must, however, not be exceeded!)

The pre-filled double-chamber syringe should not be removed from the plastic bags until shortly before use and the protective caps of the syringes should not be taken off until shortly before application.

**Administration**

The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Thawed products should be inspected visually for particulate matter and discoloration prior to administration.

Thawed, unopened pouches may be stored for up to 72 hours at controlled room temperature (not exceeding +25°C) prior to administration. TISSEEL should be warmed to 33 - 37°C.

For application of TISSEEL use the pre-filled double-chamber syringe with the Duo Set accessory devices provided with the product.

**Operating Instructions**

For application, connect the double-chamber syringe with the Sealer Protein Solution and the Thrombin Solution to a joining piece and an application needle as provided in the accompanying set of devices. The common plunger of the double-chamber syringe ensures that the equal volumes are fed through the joining piece before being mixed in the application needle and ejected.

* Connect the double-chamber syringe nozzles to the joining piece and secure it by fastening the tether strap to the double-chamber syringe. If the pull strap tears, use the spare joining piece. If none is available, further use is still possible but check that the connection is tight to prevent any risk of leaking.
* Fit an application cannula onto the joining piece.
* Do not expel the air remaining inside the joining piece or application needle until you start actual application, as otherwise the aperture of the needle may clog.
* Apply the mixed Fibrin Sealer Protein-Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

If application of the fibrin sealant components is interrupted, clogging occurs immediately in the needle. Only replace the application needle with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

Note: After mixing of the sealant components, the fibrin sealant starts to set within seconds, because of the high Thrombin concentration (500 IU/ml).

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g., endoscopic use, minimally invasive surgery, application to large or difficult-to-access areas. When using these application devices, strictly follow the instructions for Use of the devices.

After the two components have been applied, position the wound areas. Fix or hold the glued parts with continuous gentle pressure in the desired position for about 3 - 5 minutes to ensure that the setting fibrin sealant adheres firmly to the surrounding tissue.

In certain applications biocompatible material, such as collagen fleece, is used as a carrier substance or for reinforcement.
Labelling
TISSEEL Ready to use

(Calcium chloride, Aprotinin, Human fibrinogen, Human thrombin)

PL 00116/0627
TISSEEL Ready to use

Baxter

Solutions for Fibrin Sealant
For epiretinal use
Do not inject intravascularly.

1 = Component 1 = Sealer Protein Solution (1 ml)
Active Substances: Human Fibronogen (as clottable protein), 72–110 mg/ml; bovine Apolipop, 3000 KIU/ml.

2 = Component 2 = Thrombin Solution (1 ml)
Active Substances: Human Thrombin, 500 IU/ml; Calcium Chloride, 40 μmol/ml.

One pre-filled double-chamber syringe, which contains 1 ml Sealer Protein Solution with Apolipop (1 ml), deep-frozen, in one chamber and 1 ml Thrombin Solution with calcium chloride, deep-frozen, in the other chamber.

Store at -8°C (freezer). The cold storage chain must not be interrupted until used. Protect from light.

Thaw and warm the solutions before use, as directed in leaflet.

Use the thawed solutions within 72 hours. Do not refreeze or reconstitute after thawing.

Contents were sterilized and packaged under aseptic conditions.

Baxter Healthcare Ltd. UK

6108232EA01

TISSEEL Ready to use

Baxter

Solutions for Fibrin Sealant
For epiretinal use
Do not inject intravascularly.

1 = Component 1 = Sealer Protein Solution (2 ml)
Active Substances: Human Fibronogen (as clottable protein), 72–110 mg/ml; bovine Apolipop, 3000 KIU/ml.

2 = Component 2 = Thrombin Solution (2 ml)
Active Substances: Human Thrombin, 500 IU/ml; Calcium Chloride, 40 μmol/ml.

One pre-filled double-chamber syringe, which contains 2 ml Sealer Protein Solution with Apolipop, deep-frozen, in one chamber and 2 ml Thrombin Solution with calcium chloride, deep-frozen, in the other chamber.

Store at -8°C (freezer). The cold storage chain must not be interrupted until used. Protect from light.

Thaw and warm the solutions before use, as directed in leaflet.

Use the thawed solutions within 72 hours. Do not refreeze or reconstitute after thawing.

Contents were sterilized and packaged under aseptic conditions.

Baxter Healthcare Ltd. UK

6108234EA01

TISSEEL Ready to use

Baxter

Solutions for Fibrin Sealant
For epiretinal use
Do not inject intravascularly.

1 = Component 1 = Sealer Protein Solution (5 ml)
Active Substances: Human Fibronogen (as clottable protein), 72–110 mg/ml; bovine Apolipop, 3000 KIU/ml.

2 = Component 2 = Thrombin Solution (5 ml)
Active Substances: Human Thrombin, 500 IU/ml; Calcium Chloride, 40 μmol/ml.

One pre-filled double-chamber syringe, which contains 5 ml Sealer Protein Solution with Apolipop, deep-frozen, in one chamber and 5 ml Thrombin Solution with calcium chloride, deep-frozen, in the other chamber.

Store at -8°C (freezer). The cold storage chain must not be interrupted until used. Protect from light.

Thaw and warm the solutions before use, as directed in leaflet.

Use the thawed solutions within 72 hours. Do not refreeze or reconstitute after thawing.

Contents were sterilized and packaged under aseptic conditions.

Baxter Healthcare Ltd. UK

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