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Committee for Medicinal Products for Human Use (CHMP)

Consultation procedure Public Assessment Report (CPAR)

Consultation on an ancillary medicinal substance incorporated in a medical device

Medical device: Floseal Hemostatic Matrix (Floseal VH S/D)

Ancillary medicinal substance: Human thrombin VH S/D to be reconstituted in CaCl2

EMEA/H/D/000956

Applicant: TÜV SÜD Product Service GmbH

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Administrative information

Invented name of medical device:	Floseal Hemostatic Matrix (Floseal VH S/D)
INN (or common name) of the ancillary medicinal substance:	Human thrombin VH S/D to be reconstituted in CaCl2
Applicant for medical device CE certification:	Baxter Deutschland GmbH
Notified body:	TÜV SÜD Product Service GmbH
Applied intended purpose of the device:	The device is applied topically during surgery to a bleeding site as an adjunct to haemostasis when control of bleeding by ligation or other conventional procedures is ineffective or impractical. Once applied to the target site, Floseal VH S/D causes haemostatic tamponade and sealing of bleeding and provides a temporary matrix during the natural tissue repair process. The product is resorbed in vivo over a period of approximately 6 – 8 weeks.
Intended purpose of the ancillary medicinal substance in the device:	Increase the haemostatic effect
Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:	2500 IU

1. Background information on the procedure

1.1. Submission of the dossier

The Notified Body TÜV SÜD Product Service GmbH, Germany, submitted to the European Medicines Agency (EMEA) on 3 December 2007 an application for Consultation on Human Thrombin VH S/D (vapor heated, Solvent/Detergent treated) as ancillary medicinal substance used in a medical device Floseal Hemostatic Matrix (Floseal VH S/D), in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr Christian Schneider Co-Rapporteur: Dr Ian Hudson

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 3 December 2007.
- The procedure started on 27 February 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 May 2008.
- During the meeting on 23-26 June 2008, the CHMP agreed on the consolidated List of Questions to be sent to the Notified Body. The final consolidated List of Questions was sent to the Notified Body on 26 June 2008.
- The Notified Body submitted the responses to the CHMP consolidated List of Questions on 19 September 2008.
- The summary report of the inspection carried out at the following site Baxter AG, Vienna, Austria between 19-20 January 2009 was issued to EMEA on 12 February 2009.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the List of Questions to all CHMP members on 31 October 2008.
- During the CHMP meeting on 17-20 November 2008, the CHMP agreed on a List of Outstanding issues to be addressed in writing by the Notified Body.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the List of Outstanding Issues to all CHMP members on 2 February 2009.
- During the meeting on 17-19 February 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on the quality, safety and usefulness of Human Thrombin VH S/D as ancillary medicinal substance used in Floseal Hemostatic Matrix on 19 February 2009. The Notified Body provided the letter of undertaking on the recommended measures to be fulfilled post-authorisation on 13 February 2009.

2. General conditions for the use of ancillary medicinal substances in medical devices

2.1. Manufacturers

Manufacturer of the active substance used as ancillary medicinal substance

Baxter AG
Industriestraβe 131, A-1220 Vienna
Benatzkygasse 2-6, A-1220 Vienna
Austria
An inspection of this manufacturing site was carried out by the Austrian competent authority, AGES, on 19-20. January 2009. The findings of the inspection are in compliance with the Community Good Manufacturing Practice requirements.

Site where batch release takes place:

Baxter AG
Lange Allee 24, A-1220 Vienna
Austria

Manufacturer responsible for import and batch release in the European Economic Area

Not applicable

Manufacturer of the device

Baxter Healthcare Corp.
21026 Alexander Court
Hayward, CA 94545
USA

In accordance with Council Directive 93/42/EEC, as amended, a sample from each batch of bulk and/or finished product of the human blood derivative shall be tested by a State laboratory or a laboratory designated for that purpose by a Member State.

2.2. Recommended measures to the Notified Body

As discussed at CHMP, it would be recommended that the Notified Body request the following from the Applicant for device approval:

Area[1]	**Description**	**Due date**[2]
Quality	Baxter commits to introduce adequate limits for the proposed in-process controls "Determination of Protein Content" and "Determination of Factor II Content" as well as "Determination of Specific Activity" (performed on the manufacturing intermediate "Eluate") for Thrombin VH S/D bulk. These limits will be based on data from the evaluation of 15 batches Thrombin VH S/D bulk or the batches produced within one year –whatever comes first.	Approx. March 2010 – within one year after certification of the medical device Floseal Hemostatic Matrix (Floseal VH S/D)
	Baxter commits to submit an application for a type II variation/major amendment (amendments will be classified by analogy to Commission Regulation (EC) No 1085/2003) to the thrombin dossier for approval of these limits.	Approx. mid 2010
Quality	Baxter commits to evaluate the limits for Thrombin activity of Thrombin VH S/D bulk upon availability of data obtained from 15 batches Thrombin VH S/D bulk from routine.	Approx. March 2010 – within one year after certification of the medical device

		Floseal Hemostatic Matrix (Floseal VH S/D)
	Baxter commits to submit an application for a type II variation/major amendment (amendments will be classified by analogy to Commission Regulation (EC) No 1085/2003) to the thrombin dossier for approval of revised limits, if applicable.	Approx. mid 2010, if applicable
Quality	Baxter commits that – in accordance to Directive 93/42/EEC as amended by Directive 2000/70/EC each batch of human thrombin and human albumin (excipient) will be batch released by an EU OMCL.	With every batch of thrombin - permanent

1. Areas: Quality, Safety, Usefulness
2. Due date for the recommended measure or for the first interim report if a precise date cannot be committed to.

2.3. Remarks to the Notified Body

The following points were noted during the evaluation of the ancillary substance and are brought to the attention of the Notified Body for his consideration.

1. It is recommended to ask the medical device manufacturer to comment on the amount of free glutaric dialdehyde in the gelatine part of the device.

2. It is recommended to add the following sentence in the warning section of IFU: Floseal should be used with caution in neurosurgery (see section of Adverse events).

3. It is recommended to ask the medical device manufacturer to comment on the usefulness and the safety aspects of Floseal use in the neurosurgery overall. Results on efficacy in neurosurgery from C98-001 study should be provided. In addition, some safety concerns have been clearly identified, including neuro-compression, thrombotic episodes and the case of death also in the patient who underwent spinal surgery.

4. Regarding market experience of Floseal VH a few complaints could not be specified between Floseal with bovine thrombin and Floseal VH including human thrombin. What are the reasons of this identification problem? What could be done to prevent this problem to gain reliable post-marketing data in the future?

5. It is recommended to ask the medical device manufacturer to comment on the analysis of the primary end-point in C98-001 study and provide results of comparisons made in ITT population for vascular and spinal surgery.

3. SCIENTIFIC DISCUSSION

3.1. Introduction

This application concerns the initial consultation on Human Thrombin VH S/D, a plasma-derived ancillary medicinal substance used in Floseal Hemostatic Matrix (Floseal VH S/D, also referred to herein as "Floseal"), a medical device.

Floseal VH S/D is an implantable medical device that is applied topically during surgery to a bleeding site as an adjunct to haemostasis when control of bleeding by ligation or conventional procedures is ineffective or impractical. Floseal VH S/D is classified as a Class III medical device according to the Medical Device Directive (93/42/EEC), Annex IX. It incorporates animal tissue rendered non-viable

(bovine gelatine) as the agent achieving the principal intended action, haemostasis. The second component, Human Thrombin VH S/D, provides an ancillary function in supporting the haemostatic function of the gelatine matrix.

The Notified Body, TÜV SÜD Product Service GmbH, Germany, is consulting the CHMP regarding the quality, safety and usefulness of the thrombin component of Floseal VH S/D according to Directive 2000/70/EC amending Directive 93/42/EEC. Directive 2000/70/EC requires that the Notified Body consults and seeks a scientific opinion from the EMEA when a medical device incorporates, as an integral part, a human blood derivative as defined in Article 1 (4) (a) of Directive 93/42/EEC.

About the product

Floseal Hemostatic Matrix consists of two components: Gelatin Matrix (cross-linked bovine gelatine granules) and Human Thrombin VH S/D. The purpose of the incorporation of Human Thrombin as ancillary substance in the medical device Floseal is to supplement the hemostatic effect of the gelatin matrix. The medical device is manufactured by Baxter Healthcare Corp., USA, and the ancillary substance is produced by Baxter AG, Austria.

Contents of Floseal VH S/D:

Gelatin Matrix Component	Thrombin Component
- 1 x 5 mL syringe with Gelatin Matrix - 1 x 5 mL syringe with female Luer connector - 1 x bowl for Thrombin Solution - Applicator tips (2)	- 1 x 2,500 IU/vial Human Thrombin VH S/D Lyophilized - 1 x 5 mL vial of Calcium Chloride Solution - 1 x 5 mL syringe with needle attached

Human Thrombin VH S/D (2,500 IU/vial) is provided as a sterile, lyophilized, non-pyrogenic powder to be reconstituted with 5 ml sterile, non-pyrogenic Calcium Chloride Solution. The gelatin granules and the reconstituted Human Thrombin VH S/D Solution are mixed. The device is applied topically to cause tamponade and hemostasis. The product is resorbed in vivo.

In use, the gelatin matrix granules fill the wound and conform to any irregular wound geometries. The granules swell by about 20%, physically restricting the blood flow. The maximum swell volume is achieved within about 10 minutes. Blood percolates through the spaces between granules and clots. Natural clotting is induced by the gelatin matrix and accelerated by the high concentration of thrombin contained in Floseal VH S/D. Thrombin VH S/D, in addition to its role in activating coagulation factors V, VIII, and XIII and platelets, enzymatically converts fibrinogen into fibrin polymer, which forms a clot around the matrix provided by the granules. Floseal VH S/D is dependent on active bleeding as a source of fibrinogen for its activation and for formation of the clot.

The predecessor products of Floseal VH S/D are Fusion-Matrix-DRY or Floseal-DRY that contains a Gelatin Matrix Component with substantially dry cross-linked gelatin particles and a thrombin component with bovine thrombin. The latter version received a CE mark in 2002 and was the version sold in Europe from 2002 to late 2009.

Floseal Hemostatic Matrix (Floseal VH S/D) was developed to replace the bovine thrombin component in the predecessor product by human thrombin to eliminate the risk of developing antibodies to bovine thrombin and increase the safety with respect to bovine pathogen transmission.

3.2. Ancillary medicinal product before incorporation in the medical device

Introduction

Human Thrombin VH S/D is incorporated as ancillary medicinal product in the medical device Floseal to increase haemostasis. Human Thrombin VH S/D is manufactured from cryopoor supernatant. The manufacturing process includes two separate virus inactivation steps, vapour heat treatment and S/D treatment. The thrombin component contains human albumin as an excipient. The albumin is manufactured by Baxter and approved in some EU member states. The solvent is a solution containing calcium chloride as clotting activator.

General properties

Thrombin is a key enzyme of the blood coagulation system with diverse and even opposing functions.

It functions as a procoagulant enzyme by converting fibrinogen into insoluble fibrin. This process includes the enzymatic removal of fibrinopeptides A and B from fibrinogen and the activation of Factor XIII 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.

Its function as anticoagulant enzyme: 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 a prerequisite 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).

Quality Aspects

Drug Substance

- Manufacture

Manufacturer

Thrombin VH S/D Bulk is manufactured and tested by Baxter AG.

Description of manufacturing process

A sequential procedural narrative of the manufacturing process has been submitted as well as a flow diagram illustrating the purification steps from the preparation of cryosupernatant to the sterile filtration and freezing of the drug substance. The maximal holding times and temperature conditions are indicated for intermediates and drug substance. The batch size, manufacturing formula and yield are given. The applicant has provided extended information to adequately describe the manufacturing process.

Briefly, cryo-precipitate supernatant is subjected to chromatography, diafiltered, concentrated and active thrombin generated. The active thrombin is then diafiltered, concentrated and freeze dried. The vapour heat treated dried thrombin is then reconstituted in buffer and solvent detergent treated prior to further chromatography. Human albumin is added as stabiliser to the chromatography eluate which is then concentrated and forms the drug substance.

Control of materials

Human plasma is used as starting material for the production of thrombin. The collection, viral marker testing, transport and storage of single donations as well as the viral marker testing of the plasma pool is documented in the Baxter Plasma Master File (PMF) which is centrally certified through the EMA PMF certification procedure and updated through variations and annual updates.

Certificates of Analysis for the raw materials used in the manufacture of the drug substance are presented. Specifications for each raw material are established. Raw materials comply with the Ph. Eur. or where no Ph. Eur. monograph is available with national monographs.

In-process controls

The manufacturer has established in-process-controls and defined acceptance criteria at critical steps of the drug substance manufacturing process to assure that the process is controlled. A rationale is given for acceptance criteria defined. Limits set are considered acceptable. The in-process controls are considered appropriate to ensure the quality and consistency of the drug substance.

Validation

A summary of the process validation for thrombin drug substance is provided. Some manufacturing steps are covered by retrospective validation based on historical data for ten consecutive batches. A prospective process validation has been performed for the remaining manufacturing steps on three consecutive batches. Validation was performed at manufacturing scale using manufacturing equipment.

In conclusion, the submitted validation report demonstrates that all process steps in the manufacture of thrombin drug substance consistently meet their predetermined control parameters and that all in-process controls are within the established specifications.

Impurities

Process-related impurities are appropriately controlled.

Specification

Adequate specifications are set for the drug substance and sufficiently justified. Specifications defined for the process-related impurities are considered acceptable.

Appropriate analytical procedures have been selected to confirm the purity, potency, and quality of the drug substance Thrombin VH S/D Bulk. The method used for determination of thrombin activity is adapted from the method described in the Ph. Eur. (Fibrin Sealant kit. 0903). Thrombin activity (IU) is measured using the clotting time against the World Health Organization (WHO) International Standard for Thrombin (WHO #01/580).

Control Test Procedures and validation reports of the test methods provided are adequate. The rationale for the choice of the quality control tests of the drug substance is given.

Batch analysis

Results of three production scale batches are within the specifications set and provide evidence that the manufacture of the drug substance is consistent.

Container closure system

Intermediates and the drug substance are stored in containers which comply with Ph. Eur. monographs.

Stability

The stability data from three conformance lots of Human Thrombin VH S/D drug substance support the proposed shelf life.

Drug Product

Composition

The drug product, called Thrombin VH S/D Lyophilized, is formulated as a sterile, non-pyrogenic, freeze-dried, vapour-heated, solvent detergent-treated powder preparation made from pooled human plasma. It contains human plasma derived thrombin as active substance, which functions as a coagulation factor.

The drug product is to be reconstituted with the Calcium Chloride Solution and produces a solution that is referred to as the Thrombin Solution. Calcium Chloride Solution is a sterile, non-pyrogenic solution. Calcium chloride acts as clotting activator.

The finished product consists of 1 vial containing the powder preparation of Thrombin VH S/D Lyophilized and 1 vial containing the liquid preparation of Calcium Chloride Solution. Both, the drug product and the Calcium Chloride Solution are manufactured in 1ml, 2ml or 5 ml fill sizes and are sold as components of different products. For Floseal VH S/D only the 5 ml fill size of the drug product and Calcium Chloride Solution is used.

Composition Thrombin VH S/D Lyophilized and Calcium Chloride Solution

Component	Function	Reference Standard
Thrombin VH S/D Lyophilized		
Thrombin	Coagulation Factor	Ph. Eur., WHO
Protein (by addition of human albumin)	Stabilizing Agent	Ph. Eur.
Sodium Chloride	Agent to achieve Isotonicity	Ph. Eur., USP
Calcium Chloride Solution		
Calcium Chloride	Clotting Activator	Ph. Eur., USP
Water for Injections	Solvent	Ph. Eur., USP

Container closure system

The primary packaging for Thrombin VH S/D Lyophilized consists of a glass vial (5 ml fill sizes) , a fluoro-resin laminated butyl rubber stopper and a crimp cap. The glass vials and rubber stopper comply with Ph.Eur. Container closure integrity studies were performed showing that the container closure system constitutes an effective microbial barrier.

Compatibility

Thrombin solution should not be exposed to solutions containing alcohol, iodine or heavy metals because this may lead to protein precipitation and denaturation. The product should not be used in conjunction with methylmethacrylate or other acrylic adhesives. Microfibrillar collagen has been reported to reduce the strength of methylmethacrylate adhesives used to attach prosthetic devices to bone surfaces.

Heating of the reconstituted solution beyond 37°C should be avoided, which could result in denaturation of the product.

Pharmaceutical Development

The active substance of drug substance, Thrombin VH S/D Bulk, and drug product, Thrombin VH S/D Lyophilized, is human plasma-derived thrombin. The pharmaceutical development of the drug substance mainly focused on viral safety and purity. Human albumin is added as stabiliser.

The drug product contains a human thrombin of high purity. During the pharmaceutical formulation the concentrations for thrombin, human albumin, and sodium chloride are adjusted according to the specifications.

Description of manufacturing process

A flow diagram for the drug product manufacture has been provided and the process has been described in sufficient detail. Briefly, it comprises of the following steps: formulation, sterile filtration, sterile filling, freeze-drying as well as quality control and labelling and packaging. Minimum and maximum batch formula are given.

In-process controls

In-process controls are adequately set and justified.

Validation

Validation studies document that formulation, filling and lyophilisation consistently adhere to predetermined specifications. Seven conformance lots representing three fill sizes were manufactured to demonstrate process consistency. Deviations which occurred during production of conformance lots were discussed. They were considered not critical for product quality and thus accepted for validation.

Control of excipients

Human albumin and sodium chloride are included as excipients in the composition of the drug product. Both conform to the respective Ph Eur monographs.

Albumin is used as a stabilizer in the thrombin formulation and is the manufacturer's licensed, pasteurised albumin (Human Albumin 200 g/l IMMUNO). Human Albumin 200 g/l IMMUNO is a sterile, non-pyrogenic aqueous solution of human albumin complying with the requirements of Ph. Eur. with an albumin content of at least 95%. It is manufactured according to the Cohn fractionation by Baxter from source plasma described in the same PMF as Human Thrombin VH S/D (see below).

Baxter states that only albumin is used in the manufacture of Thrombin VH S/D Lyophilized that is within its shelf life and that is batch released by an OMCL.

Product Specification

Specifications were defined for the drug product and appropriate test methods according to Ph. Eur. established. Specifications comply with the current Ph. Eur. monograph. Method validations have been

provided for the release tests performed on the drug product. Determination of Thrombin Activity and Protein Content are adaptations of the respective Ph. Eur. methods.

There are no new impurities introduced in the manufacture of the drug product.

Batch analysis

Results of batch analyses from production-scale conformance lots meet predetermined specifications and document consistency in the manufacture of thrombin drug product.

Stability of the Product

The applicant provided stability data for 36 months storage at +2°C to +8°C and +25°C for lyophilised thrombin (2,500 IU/vial). All results for the thrombin activity comply with the predefined specification supporting the proposed shelf life of 3 years at up to +25°C.

According to ICH guideline Q5C the stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified. Recent results of stability studies of three lots of the reconstituted product covering an incubation period of 36 hours at room temperature after the shelf life of 3 years of the lyophilized product at +25°C have been provided. Results presented are within the predefined specifications supporting the claimed in-use shelf life of 4 hours at +25°C for reconstituted Thrombin VH S/D.

In accordance to Directive 93/42/EEC as amended Baxter stated that the thrombin component will be batch released by an EU OMCL.

In-use stability of the reconstituted Thrombin Solution has been demonstrated for 4 hours at room temperature. Reconstituted product must not be returned to the refrigerator or frozen.

Virus Safety

Thrombin VH S/D is manufactured from human plasma. The potential contamination of plasma pools with HIV, HBV, HCV, HAV, and B19V is limited by testing of individual donors according to the requirements, by testing of mini-pools and plasma pools for fractionation for viral nucleic acids. Donors with an increased risk for sporadic or variant Creutzfeldt-Jakob-Disease are excluded. Two steps have been implemented in the manufacturing process of the Thrombin VH S/D component in order to inactivate/remove viruses. Validation studies were performed according to Guideline CPMP/BWP/268/95. Enveloped viruses are effectively inactivated. In addition, the non-enveloped Hepatitis A virus was effectively inactivated.

The animal model parvovirus MMV was not inactivated. The justification can be accepted. With the response to the LoI D180 a revised risk assessment according to CPMP/BWP/5180/03 was submitted. Taking all measures together, i.e. B19V screening at the plasma pool level and the overall B19V reduction capacity of the process, the B19V safety margin for the Thrombin component of Floseal is considered appropriate. Therefore, the statement included in the "Instructions for Use" (warnings) "The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19" is acceptable. It is in compliance with the Note for Guidance on the Warning on Transmissible Agents in Summary of Product Characteristics (SPCs) and Package Leaflets for Plasma-derived Medicinal Products (CPMP/BPWG/BWP/561/03).

In summary, virus safety of Thrombin VH S/D has been adequately demonstrated. No animal-derived TSE-risk material which is added at Thrombin VH S/D production was identified. Reduction of human TSE agents for the Thrombin VH S/D and the Albumin to comply with CHMP position statement on Creutzfeldt-Jakob disease & plasma-derived and urine-derived medicinal products

(EMEA/CPMP/BWP/2879/02/rev 01) has been demonstrated. Albumin produced from human plasma is added during production of Thrombin VH S/D. Adequate viral inactivation/removal capacity of the manufacturing process of Albumin has been demonstrated. With the response to the LoI D180 adequate information was provided on porcine heparin which is used in small amounts only in the early manufacturing steps of the Albumin process and is thus subjected to all the virus reduction steps of the Albumin process.

Calcium Chloride Solution: Diluent for Reconstitution

The documentation of the Calcium Chloride Solution comprises manufacture of the solvent including dissolution of calcium chloride dihydrate in Water for Injection, sterile filtration, filling into vials and autoclaving.

Results of the validation studies for critical steps including product-specific validation of the thermal sterilization process, filter integrity tests and microbiological leak testing of the container have been submitted.

Validation studies for this assay have been presented. Validation summaries for the analytical procedures used in the quality control for release of Calcium Chloride Solution have been provided as well.

According to stability guideline ICH Q1E extrapolation of the available data supports the proposed shelf life.

Human Albumin

Introduction

Human Albumin is used as stabiliser of human thrombin. It is a sterile, non-pyrogenic aqueous solution of human albumin complying with the requirements of Ph. Eur. with an albumin content of at least 95%. It is manufactured according to the Cohn fractionation from source plasma described in the same PMF as Human Thrombin VH S/D.

A complete Module 3 on the production of the human albumin was provided and assessed as containing sufficient information to adequately document the quality of the human albumin.

It is confirmed that only albumin is used as stabiliser for human thrombin which is within its shelf life and which is batch released by an OMCL.

Drug Substance

- Manufacture

Manufacturer

Human Albumin 200 g/l IMMUNO is produced by Baxter AG, Austria.

Description of manufacturing process

A detailed description as well as a flow chart of the manufacturing process of Human Albumin drug substance has been provided.

Briefly, quality control released plasma is thawed and cryoprecipitate is removed by centrifugation. This is followed by adsorption of the cryosupernatant. Albumin is isolated by three subsequent cold

ethanol precipitation. Inorganic substances and components of low molecular weight are then separated from the intermediate.

Control of materials

Human plasma is used as starting material for the production of albumin. The collection, viral marker testing, transport and storage of single donations as well as the viral marker testing of the plasma pool is documented in the Baxter Plasma Master File (PMF) which is centrally certified through the EMA PMF certification procedure and updated through variations and annual updates.

Certificates of Analysis for the raw materials used in the manufacture of the drug substance are presented. Raw materials comply with the Ph. Eur. or where no Ph. Eur. monograph is available with national monographs.

In-process controls

The manufacturer has adequately established in-process-controls and defined acceptance criteria at critical steps of the drug substance manufacturing process to assure that the process is controlled.

Validation

The cold ethanol fractionation procedure has been used for a long time for the manufacture of Human Albumin. Comparative batch release data show the consistency of the manufacturing process.

Specification

Specifications for the drug substance are adequately set and justified.

The methods used for quality control of the drug substance are Ph.Eur. methods. Summaries of the method validation reports were provided and are considered appropriate.

Batch analysis

Results of the batch analysis data of 10 consecutive batches demonstrate consistency of the manufacturing process within specification limits.

Container closure system

The transport container is a stainless steel pressure tank.

Drug Product

Composition

Human Albumin 200 g/L Immuno is presented as a solution for intravenous infusion complying with the requirements of Ph. Eur.

Description of manufacturing process

The manufacturing process of the drug product is described in sufficient detail. It comprises the following steps: dilution of the drug substance bulk, addition of stabilisers, sterile filtration, filling and pasteurisation. The batch formula has been provided. Adequate in-process controls are established.

Validation

The summary of the validation studies of the manufacturing process of the drug product Human Albumin 20% Immuno documents a consistent production process leading to a final product within defined specifications.

Control of excipients

The excipients used for the manufacture of Human Albumin 200 g/L Immuno meet Ph. Eur standards.

Product Specification

Adequate specifications are defined for the drug product and appropriate test methods are established according to Ph. Eur.

All analytical methods used for the quality testing of the drug products are EP-methods. Summaries of the method validation reports are provided and are considered appropriate.

Container closure systems

The containers used for the packaging of the final product are in accordance with the current version of the Ph.Eur. (3.2.1.Glass Containers for Pharmaceutical Use).

Rubber stoppers used as closures meet the requirements of the actual version of the Ph. Eur. (3.2.9.Rubber Closures for Containers for Aqueous Preparations for Parenteral Use).

Stability

According to the stability data presented in the dossier, storage conditions of Human Albumin Solution 20% at a temperature of +2°C to +8°C for 60 months are considered acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product of the ancillary medicinal substance Human Thrombin were presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the ancillary medicinal substance should have a satisfactory and uniform performance in the clinic. Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

3.3. Medicinal product in the context of its use in the medical device

Introduction

Quality, Safety and Usefulness

- General Information

Floseal Hemostatic Matrix ("Floseal VH S/D", also referred to herein as "Floseal") is an implantable medical device. As supplied by the medical device manufacturer, Baxter AG, to the end user, each carton of Floseal contains two main sterile components:

1) Gelatin Matrix (cross-linked bovine gelatin granules)

2) Human Thrombin VH S/D

Also included are applicator tips and several accessories to facilitate the reconstitution and preparation of the product and to facilitate the delivery of the product to the site to be treated, as well as instructions for preparing the product for use. The device is provided in the configuration shown in the table below:

Contents of Floseal VH S/D	
Gelatin Matrix Component	**Thrombin Component**
1 x 5 mL syringe with Gelatin Matrix 1 x 5 mL syringe with female Luer connector	1 x 2,500 IU/vial Human Thrombin VH S/D 1 x 5 mL vial of Calcium Chloride solution

1 x bowl for Thrombin solution Applicator tips (2)	1 x 5 mL syringe with needle attached

Floseal Hemostatic Matrix (Floseal VH S/D) was developed with the objective to further improve the safety profile of the predecessor product Floseal currently on the market in European countries. While the gelatin matrix remains unchanged, bovine thrombin will be replaced by human thrombin, thus eliminating the risk of development of antibodies to bovine thrombin and further increasing the safety margin with respect to bovine pathogen transmission. The Gelatin Matrix of Floseal VH S/D consists of gelatin granules of bovine origin crosslinked by glutaraldehyde, and is provided sterile and non-pyrogenic in a standard disposable 5 ml syringe. The purpose of the inclusion of human thrombin is to supplement the hemostatic effect of the gelatin matrix.

Gelatin and Thrombin are mixed in the operating room prior to use. For that purpose, lyophilized Thrombin VH S/D is reconstituted by adding the supplied calcium chloride diluent to the thrombin powder. The reconstituted Thrombin VH S/D is then thoroughly mixed with the Gelatin Matrix.

Floseal is indicated in invasive or surgically invasive procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

- Qualitative and quantitative particulars of the constituents

The thrombin component of Floseal consists of 1 x 2500IU/vial human thrombin and solvent 1 x 5ml vial of sterile Calcium Chloride Solution, and a 1 x 5ml syringe with needle is attached. The thrombin is re-dissolved in the Calcium Chloride Solution and the re-dissolved thrombin is then used to hydrate the gelatin matrix beads.

- Description of method of manufacture

For the manufacture of Floseal, the primary packaging of components, the ancillary medicinal product, human thrombin, and the device, bovine gelatine, is carried out separately. Subsequently, both components are placed into a carton with the Instructions for Use for marketing.

- Controls of starting materials

See above section 3.2 Medicinal product before incorporation in the medical device

- Control tests carried out at intermediate stages of the manufacturing process of the medical device

See above section 3.2 Medicinal product before incorporation in the medical device

- Control tests on finished product

See above section 3.2 Medicinal product before incorporation in the medical device

- Stability

The claimed shelf-life for Floseal is 2 hours. Data supporting the in-use shelf life of Floseal have been provided.

- Toxicity

Toxicity testing for Floseal VH S/D comprised biocompatibility studies conducted according to the requirements of ISO 10993 (cytotoxicity, biodegradation, impurities, intracutaneous reactivity and delayed dermal contact sensitisation) and local tolerance tests described later in this report. For certain aspects of the ISO 10993 testing (hemocompatibility, acute systemic toxicity and pyrogenicity), use of thrombin would interfere with the test, hence the thrombin solution was replaced by saline solution in preparing the test article. These aspects of the ISO testing are not relevant for assessing the ancillary

substance. Overall, the results from testing of Floseal VH/SD and of the gelatine component without the addition of any thrombin demonstrate the biocompatibility of Floseal VH/SD according to ISO standards, hence no toxicity issues are raised concerning the ancillary substance (thrombin VH S/D).

- Reproductive function

Data on reproductive toxicity have not been provided, which is considered acceptable for this type of product.

- Embryo/foetal and perinatal toxicity

Data on embryo- and fetal toxicity have not been provided, which is considered acceptable for this type of product.

- Mutagenic potential

Relevant studies were conducted according to the requirements of ISO 10993 for genotoxicity. Floseal VH S/D was not found to be mutagenic.

- Carcinogenic potential

Data on carcinogenicity have not been provided, which is considered acceptable as the product is unlikely to be carcinogenic.

- Pharmacodynamics

Support for the clinical efficacy of Floseal was based on a clinical study conducted using Floseal-WET, a predecessor version of the product. It was therefore necessary to examine the equivalence in terms of hemostatic efficacy of subsequent versions of the product to Floseal-WET in non-clinical studies. These versions were:

- Fusion-Matrix-DRY or Floseal-DRY containing a Gelatin Matrix Component with substantially dry cross-linked gelatin particles and a Thrombin Component with bovine thrombin. This only differs from Floseal-WET in that Floseal-WET contains hydrated (as opposed to dry) gelatin particles.

- Floseal VH containing the DRY matrix and human thrombin subjected to vapour/heat viral inactivation. This only differs from Floseal VH S/D in that the thrombin in Floseal VH S/D is also subjected to solvent/detergent viral inactivation.

Three preclinical studies were performed to compare the performance of the new Floseal VH S/D device to its predecessors, the performance of different thrombin variants, and the hemostatic efficacy of the individual ingredients of the device (per Guidelines on Medical Devices, MEDDEV 2.7.1).

Equivalence of Floseal-WET and Floseal-DRY

Design

In preclinical study P00-017, the hemostatic performance of Floseal-WET and Floseal-DRY was assessed in 3 heparinized pigs. Floseal-WET and Floseal-DRY were prepared per IFU using bovine thrombin. In 3 anesthetized pigs, laparotomy was performed and the liver was exposed and isolated. Heparin was administered such that the activated clotting time was maintained at a level of 3 to 5 times baseline throughout the experiment. A series of square lesions (approximately 1 cm x 1 cm x 0.3 cm) was created on the liver surface using sharp dissection. The first and last lesions were not treated and served as a control. Subsequent lesions were created in pairs and treatment applied in a random fashion. Bleeding was scored at 3, 6 and 10 minutes. At the end of the study, the animals were euthanized.

Results

The blood flow rates for the untreated control lesions averaged 2.39, 3.92 and 2.64 mL/min at 3, 6 and 10 min respectively. The average blood flows following treatment with Floseal-DRY were 0.02, 0.05 and 0.00 mL/min at the same time points. The average blood flows for lesions treated with Floseal-WET at the same times were -0.01, 0.01 and 0.02 mL/min, respectively. These data were analysed using the method of Blackweller and Chang modified for use with continuous variables. The p-value for testing equivalence between Floseal-DRY and Floseal-WET for each of the time intervals was less than 0.001. To support the assumption of independence of the data within an animal for the above analyses, the intra-class correlation coefficient based on the factors of animal and treatment was computed. The coefficient was 0.034, 0.000 and 0.049 at 3, 6 and 10 min, respectively.

Floseal

Comparative Evaluation of the Acute and Sustained Hemostatic Performance of Floseal VH S/D, Floseal VH and Floseal

Design

In a rabbit liver punch model (preclinical study PV1780602), the performance of Floseal VH S/D (with human Thrombin VH S/D), Floseal VH (with human Thrombin VH) and Floseal (with bovine Thrombin-JMI) in terms of time to hemostasis, rebleeding, 24 h survival, 24 h rebleeding and amount of rebleeding was evaluated in relation to a standard topical hemostat - gelatin sponge (Spongostan). Anesthetized, severely heparinized (>10 x the normal human dose of heparin during surgery) rabbits received plasma expander infusion to dilute coagulation factors, underwent median laparotomy and standardized fully penetrating lesions were placed in the liver using punches. The 3 Floseal variants were reconstituted according to the IFU and then applied to the lesions by a surgeon who was blinded to the identity of the Floseal variant used. Spongostan sponge was applied as control treatment. Animals in which hemostasis could not be achieved were sacrificed. The remaining animals were observed for rebleeding and sacrificed after 24 h.

Results

In the 3 groups that received one of the variants of Floseal (12 animals per group), hemostasis within 15 minutes was achieved in all but 1 animal (in the Floseal VH S/D group), while only 1 of 15 animals achieved hemostasis in the control group. Time to hemostasis was significantly shorter ($p<0.0001$) in each of the 3 Floseal groups than in the control group. The percentage of animals bleeding at 15 minutes post product administration was significantly lower ($p<0.0001$) in each of the 3 Floseal groups compared to the control group. In the 3 Floseal groups taken together, all animals but 1 (of 12 per group) survived 24 h while in the control group only 1 of 15 animals survived. Twenty-four hour survival per Floseal group was thus significantly higher ($p<0.0001$) compared to survival in the control group.

Rebleeding within 24 h occurred in 66.7% of the animals in the group that had received Floseal with bovine Thrombin-JMI, 50% of the animals in the Floseal VH group and 36.4% of the animals in the Floseal VH S/D group. The median rebleeding volumes in the 3 Floseal groups were 4.9 g for Floseal with bovine Thrombin-JMI, 1.2 g for Floseal VH and 0.0 g for Floseal VH S/D. The only remaining animal in the control group experienced rebleeding of a volume of 6.3 g in the 24 h follow-up period.

Comparative Evaluation of Human and Bovine Thrombin for Use in Floseal

Design

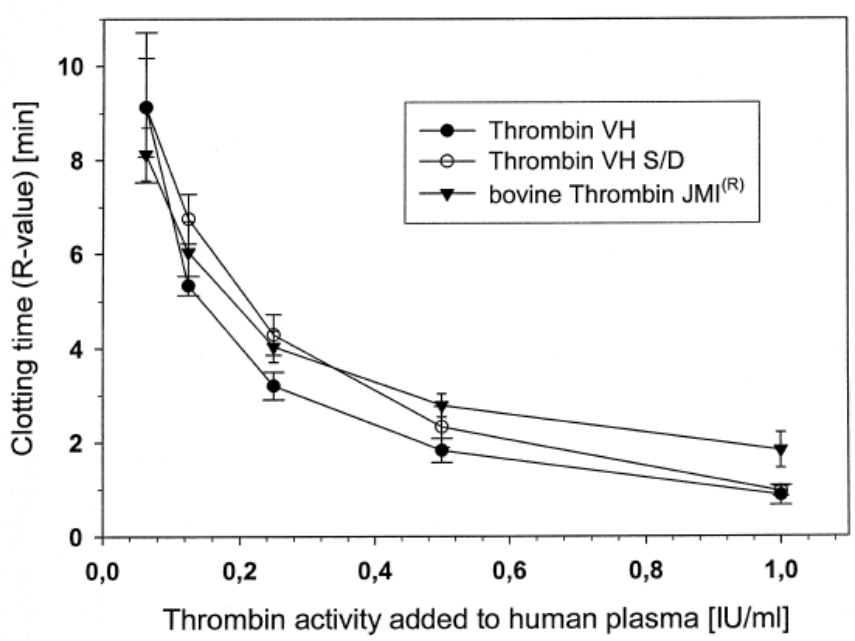
Thromboelastography measures the kinetic of clot formation and the strength of the formed clot in an oscillating cup. This cup is filled with the clotting solution and a pin suspended by torsion wire is placed in the middle of the cup. As the cup oscillates and the solution thickens, the pin is put into motion relative to the strength of the forming clot. In study PV1750506, the rate of clot formation at 37° C

was compared among 3 different types of thrombin: human Thrombin VH (500 IU/mL), human Thrombin VH S/D (500 IU/mL) and bovine Thrombin-JMI (1,000 US units/mL). All 3 variants were reconstituted according to label instructions and subsequently diluted with a thrombin dilution solution (200 mM CaCl2, 3mg/mL human albumin) in 5 concentrations between 0.625 and 10 IU thrombin/mL. 50 µL of each dilution were added to 450 µL of citrated human plasma. Reaction time to the first significant, detectable levels of clot formation was measured.

Results

Clotting times after addition of human plasma were similar for all 3 variants of thrombin in all concentrations evaluated (see figure below).

Figure: Dependence of Clotting Time of Human Plasma on the Concentration of Added Thrombin



For each thrombin variant, 3 lots were run in duplicate. Means (n=6) ± standard deviations are shown.

Evaluation of the Hemostatic Performance of Floseal (with Thrombin), Floseal (without Thrombin), and Thrombin Topical

Design

In preclinical study P04-010, the hemostatic performance of Floseal VH (Gelatin Matrix and human thrombin VH), Gelatin Matrix alone, and topical human thrombin alone was assessed in 3 heparinized pigs. Lyophilized human thrombin (2,500 IU) was reconstituted with 5 mL of calcium chloride solution (40 µmol/mL). Floseal was prepared per IFU using human thrombin VH. The Gelatin Matrix was also prepared per IFU using 0.9% sodium chloride solution (4 mL liquid) alone instead of reconstituted thrombin.

In 3 anesthetized pigs, laparotomy was performed and the liver was exposed and isolated. Heparin was administered such that the activated clotting time was maintained at a level of 3 to 5 times baseline throughout the experiment. A series of square lesions (approximately 1 cm x 1 cm x 0.3 cm) was created on the liver surface using sharp dissection. The first and last lesions were not treated and

served as a control. Lesions were created in series of 3 and treatment applied in a random fashion. Bleeding was scored at 0, 6 and 12 minutes. At the end of the study, the animals were euthanized.

Results

In the analysis initially performed, bleeding from each lesion was scored on a scale from 0 (none) – 4 (severe), with a score of ≤1 considered as treatment success. Floseal and Gelatin Matrix alone were found to be statistically significantly better than thrombin alone at achieving hemostasis in this model. Floseal had a 100% success rate at the 12-minute evaluation, whereas a success rate of 94% was observed for the Gelatin Matrix. The success rate for thrombin solution was 38.9%. No difference in hemostatic performance between Floseal and Gelatin Matrix was seen at 6 minutes (100% each), the success rate of thrombin was 48%. When a more strict definition of success was applied (a score of ≤0.5), the success rate of Gelatin Matrix dropped to 77.8% and 72.2% for the 6- and 12-minute evaluations with no change in the success rate of Floseal (100%), while thrombin was virtually non-effective with 16.7% and 11.1% success at 6 and 12 minutes, respectively.

- Pharmacokinetics

Data on pharmacokinetics have not been provided. This is acceptable as the product is applied topically and has no systematic action. Moreover, efficient endogenous thrombin inactivation mechanisms ensure that the action of the applied thrombin remains local. In agreement with this, adverse events from systemic circulation of thrombin have only been observed upon direct intravascular injection and few adverse events due to systemic thrombin action have been observed despite the variability of the amount of Floseal used in different surgical procedures.

- Local tolerance

Local tolerance was studied in nonclinical studies which in first line were designed to evaluate differences in local tissue reaction between Baxter´s vapour heated Fibrin Sealant VH and the double virus inactivated Fibrin Sealant VH S/D (vapour heat treated + solvent detergent treated). The studies were performed using the final product, meaning a mixture of Thrombin+Calcium chloride (as used as ancillary medicinal substance in Floseal VH S/D) and Sealer Protein+Aprotinin. More specifically, four comparative in-vivo studies were performed in rats and rabbits using a subcutaneously implanted spongiosa block model (study numbers PV0030002, PR250008, PV0020002, PR260008). Granulation tissue formation, residual fibrin, inflammation and foreign body reaction were evaluated.

In the rat studies there was no statistically significant difference between Fibrin Sealant VH S/D (= vapour heat treated + solvent detergent treated Fibrin Sealant), Fibrin Sealant (Baxter`s vapour heat treated Fibrin Sealant with high amounts of FXIII) and Fibrin Sealant VH (Baxter`s vapour heat treated Fibrin Sealant with low amounts of FXIII) with regard to the parameters evaluated. No animal had more than a mild foreign body reaction with any of the preparations. Residual human fibrin, as expected as a reaction to the injection of a heterologous protein, and inflammatory signs, which represent a natural part of the wound healing process, were observed, but in both products responses were mild to medium. 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 approach of using the substance in the context of a different device is acceptable, as any issue with regard to local tolerance of Thrombin VH S/D would have been detected.

- Clinical documentation

The Applicant has not performed a clinical study with Floseal VH S/D. The usefulness and safety of Floseal VH S/D as an adjunct to haemostasis is supported by two clinical studies (main study C98-001 and supportive study C99-001) of a predecessor product (Fusion Matrix-WET with bovine thrombin), summarised in the following table:

Study number	Title	Study design	Conclusions
C98-001 (registration study Fusion Matrix WET)	Evaluation of Fusion Matrix, a Novel Haemostatic Sealant, for Stopping Intraoperative Bleeding	Prospective, randomized, controlled, multicenter (10 sites), 309 patients (cardiac, vascular or spinal/orthopaedic surgery)	1. Fusion Matrix-WET was more effective at achieving haemostasis within 10 minutes than Gelfoam+Thrombin. 2. Time to cessation of bleeding was statistically significantly shorter with Fusion Matrix-WET. 3. Fusion Matrix was as safe as Gelfoam+Thrombin. Similar increase in antibody titers to bovine thrombin or bovine factor V_a. No evidence of antibody-related coagulopathies.
C99-001	Pre-marketing study of Fusion Matrix WET	Single-arm, multicenter (2 sites), 29 patients (spinal/orthopaedic surgery)	1. Fusion Matrix-WET was recorded safe and effective 2. Surgeons` perception was very positive 3. In 86% of applications, Fusion Matrix-WET was judged to be better than the alternative haemostatic agents that the surgeon may have used.

Moreover, the Applicant provided a literature review, also largely limited to Floseal containing bovine thrombin. As the human origin Thrombin VH S/D is not sold on the market as a stand alone product, but only as a component of fibrin sealant VH S/D with 500 units thrombin VH S/D and 4 units thrombin VH S/D, the Applicant also provided literature references relevant to these products. Finally, clinical safety data are gained from US market experience of Floseal VH (human thrombin) and clinical data of Thrombin VH (pharmacovigilance, clinical studies) and Thrombin VH S/D (clinical studies) as components of Baxter`s fibrin sealants.

Clinical studies

Study C98-001

Study Design

This prospective, randomized, controlled clinical study was designed to evaluate the efficacy and safety of Fusion Matrix-WET compared to a control treatment (gelatin sponge [Gelfoam] soaked with bovine thrombin) in controlling intraoperative bleeding. The study objective was to show equivalence between Fusion Matrix-WET and the control product. The primary efficacy endpoint was the proportion of subjects who achieved hemostasis at the first lesion treated within 10 minutes of treatment. Secondary efficacy endpoints were: proportion of lesions treated for which hemostasis was achieved within 10 minutes and the actual time to hemostasis after treatment of the first lesion and of all lesions. Product safety was determined by comparing AEs that occurred post-surgery, as well as out of reference range blood test results (hematology, coagulation, and blood chemistry tests) at 24 h (12-36 h) post-surgery and 6-8 weeks post-surgery and the number of patients that developed antibodies to bovine thrombin and bovine factor Va between the Fusion Matrix-WET and the control group.

Patients were divided into 3 cohorts based on the type of surgery performed: Cardiac, vascular and spinal/orthopedic. Subjects were randomized on the day of surgery.

Study Population

In clinical study C98-001, 309 subjects were enrolled and randomized. 156 were randomized to Fusion Matrix-WET and 153 were randomized to the control (gelatin sponge soaked with thrombin) group. The baseline demographic characteristics in both the Fusion Matrix-WET and the control group were comparable for gender and age. Enrollment was evenly distributed among the cardiac, vascular, and spinal/orthopedic cohorts.

Efficacy Results

Results for the primary endpoint are shown in the following table:

Treatment Success by Surgical Specialty: First Lesion Only Hemostasis Within 10 Minutes (Intent-to-Treat) (Study C98-001)

Patient Category	Fusion Matrix	Gelatin Sponge soaked with thrombin	p-value[a]
All Patients	96% (149/156)	77% (118/153)	<0.001
Cardiac	94% (45/48)	60% (27/45)	<0.001
Vascular	93% (40/43)	76% (35/46)	0.036
Spinal//Orthopedic	98% (64/65)	90% (56/62)	0.042

a p-values from Cochran-Mantel-Haenszel test for row mean scores, adjusted for study site.

Results for the endpoint of success/failure to achieve hemostasis at 10 min for all lesions are summarized below:

Treatment Success by Surgical Specialty: All Lesions Hemostasis Within 10 Minutes (Intent-to-Treat) (Study C98-001)

Patient Category	Fusion Matrix	Gelatin Sponge soaked with thrombin	p-value[a]
All Patients	95% (357/377)	83% (267/323)	<0.001
Cardiac	88% (92/104)	57% (35/61)	<0.001
Vascular	92% (86/93)	73% (73/92)	0.010
Spinal//Orthopedic	99% (179/180)	93% (158/170)	0.001

Results for the endpoint of time to hemostasis are summarized in below:

Median Time to Hemostasis by Surgical Specialty: First Lesion Only (Study C98-001)

Patient Category	Median Time to Hemostasis in Minutes (95% CI[a])	
	Fusion Matrix-WET	Control
All Patients	2.0 (1.5, 2.5)	6.0 (5.5, 6.0)
Cardiac	2.8 (2.0, 4.0)	8.0 (6.0, 8.5)
Vascular	2.5 (2.0, 4.0)	6.5 (4.5, 8.0)
Spinal/Orthopedic	1.5 (1.0, 1.5)	3.0 (2.0, 4.5)

a Confidence Interval using a Bonferroni correction.

Similar results were obtained for time to hemostasis when the first and subsequent lesions treated were included in the analysis.

Safety Results

A total of 384 AEs were reported in 165 patients.

Table 7-19 (Cont'd)
Summary of Adverse Events (Intent-to-Treat)

	Fusion Matrix	Control	Total
Number of Patients	156	153	309
Number of Patients Reporting Events	80 (51%)	85 (56%)	165 (53%)
Number of Events Reported	192	192	384
Body System[a]			
Cardiovascular System	38 (24%)	41 (27%)	79 (26%)
Body as a Whole	24 (15%)	31 (20%)	55 (18%)
Respiratory System	18 (12%)	20 (13%)	38 (12%)
Nervous System	17 (11%)	15 (10%)	32 (10%)
Hemic and Lymphatic System	15 (10%)	13 (8%)	28 (9%)
Urogenital System	11 (7%)	10 (7%)	21 (7%)
Digestive System	8 (5%)	12 (8%)	20 (6%)
Skin	11 (7%)	8 (5%)	19 (6%)
Metabolic/Nutrition Disorders	8 (5%)	5 (3%)	13 (4%)
Musculoskeletal System	1 (1%)	5 (3%)	6 (2%)
Immune System	2 (1%)	1 (1%)	3 (1%)
Special Senses	0 (0%)	3 (2%)	3 (1%)
Connective Tissue	1 (1%)	1 (1%)	2 (1%)

[a] Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to a Modified COSTART 5th edition body system. At each level of summarization (body system or event) patients are only counted once. Percentages of patients in each treatment group are also given.

The distribution of all adverse event incidences by SOC class was not imbalanced between two groups. 97% of all AEs were reported as "Not related".

There were a total of 16 deaths, 5 in the Fusion Matrix group and 11 in control group. 13 deaths occurred during the 6-8 week follow-up period, and 3 occurred after the patients had exited the study as a result of complications identified during follow-up period. The 5 patients who died in the Fusion Matrix group were all cardiac patients. Of the 11 patients assigned to the control group who died, 5 were cardiac surgery patients, 1 was a spinal/orthopaedic surgery patient, and 5 were vascular surgery patients.

None of AEs were reported by the surgeon to be "probably related" to the use of either haemostat.

The results of haematology and chemistry blood tests were within the acceptable range and in accordance to the severity of peri- and post-operative condition of patients.

The summary of antibody testing is provided in the table below:

Table 7-24
Titers of Antibodies

Variable	Fusion Matrix	Control	P-Values
Number of Patients	156	153	
Thrombin Titer			
Increase	25 (18%)	26 (20%)	0.757
No Increase	114 (82%)	105 (80%)	
Not Reported*	17	22	
Factor V_a Titer			
Increase	39 (28%)	43 (33%)	0.428
No Increase	100 (72%)	88 (67%)	
Not Reported*	17	22	

* - Includes patients whose blood was not drawn or who expired.
P-values obtained from a Fisher's Exact test.

- Increase in titer was defined as Baseline (-) to Follow-up (+).
- No Increase in titer was Baseline (-) to Follow-up (-).
- For patients with a Baseline (+) to Follow-up (+), semi-quantitative titers were used to determine Increase or No Increase in titer.
- No patients were seen with a decrease in titer between Baseline and Follow-up.

As is evident from the table, the titers of antibodies against Thrombin and Factor V were increased in both arms of the study. There were no patients who were positive for antibodies and had elevated prothrombin times who were not taking anticoagulant medications. There was no evidence of any antibody-induced coagulopathies in the present study. There were 3 reports of patients with either coagulopathy or hypercoagulable state: 2 in the Fusion matrix group and 1 in Control group. They were all considered unrelated to the haemostat.

Study C99-001

Study Design

Study C99-001 is a single-arm, multicenter study which was to enroll patients undergoing surgical procedures other than neurosurgery, urologic surgery, or ophthalmic surgery. As the study was terminated prematurely, only patients who underwent spinal/orthopedic surgery were included.

The objectives of the study were to identify the surgeons' perceptions of the value of Fusion Matrix-WET, to understand if these perceptions changed during the first 5 uses of Fusion Matrix-WET, and to quantify the number of Fusion Matrix-WET kits routinely used for different procedures.

The efficacy of Fusion Matrix-WET was documented by periodically recording whether bleeding had stopped, was substantially reduced, somewhat reduced, or whether Fusion Matrix-WET was not effective. The surgeon's perception of the use of Fusion Matrix-WET was determined through a series of questions and the number of Fusion Matrix-WET kits used was recorded. Adverse device effects were documented and graded by severity (mild, moderate, severe) and relationship of effect to the use of Fusion Matrix-WET (not related, possibly related, probably related).

Study Population

In study C99-001, enrollment of up to 100 adult patients had been planned. However, the study was terminated prematurely after 29 patients had been enrolled, because the US FDA approved the device before the study was completed. All 29 patients underwent spinal/orthopedic surgery, and all 29 patients completed the final follow-up. Nineteen (65.5%) patients were male with a mean age of 60.5

(range 30 – 81) years; and 10 (34.5%) patients were female with a mean age of 50.1 (range 28 – 71) years.

Efficacy Results

Results on the evaluation of bleeding control at the primary treatment site are presented below:

Effectiveness of Fusion Matrix-WET (1st Application Site) (Study C99-001)	
How Well was Bleeding Controlled?	**Number of Subjects (%)**
Stopped completely	22/29 (75.9%)
Reduced substantially	7/29 (24.1%)
Reduced slightly	0/29 (0%)
No change in bleeding	0/29 (0%)

The performance of Fusion Matrix-WET was consistently judged to be better than the performance of alternative hemostatic agents that might have been used if Fusion Matrix-WET had not been available ($p<0.001$, Sign Test, results in the table below). These agents included Gelfoam + thrombin, Gelfoam Powder, and Fibrillar Surgicel.

Performance of Fusion Matrix-WET Relative to Alternative Hemostatic Agents (Study C99-001)	
Performance Relative to Alternative Hemostatic Agents	**Number of Responses (%)**
Better than	25/29 (86.2%)
Same as	3/29 (10.3%)
Worse than	1/29 (3.5%)

Each of the 6 surgeons who enrolled patients had used Fusion Matrix-WET at least 5 times previously. The surgeons' perception of Fusion Matrix-WET remained positive and did not change during the first 5 uses in surgery. All surgeons stated that they would recommend Fusion Matrix-WET to colleagues.

An average of 1.45 kits of Fusion Matrix-WET was used per patient. There did not seem to be a correlation between the different procedures and the amount of Fusion Matrix-WET used. However, all patients in this study underwent spinal/orthopedic procedures.

Safety Results

A total of 28 AEs were recorded in 15 out of 29 patients. All AEs were considered as "not related".

Table 1-7
Detailed Listing of Adverse Events

	FloSeal Treated
Number of Patients	29
Number of Patients Reporting Adverse Events	15 (52%)
Number of Adverse Events Reported	28
Adverse Event	
Fever	10 / 29 (34.5%)*
Rash/Itching	4 / 29 (13.8%)*
Nausea & Vomiting	2 / 29 (6.9%)*
Pain	2 / 29 (6.9%)*
Urinary Retention	2 / 29 (6.9%)*
Decreased Consciousness/Respiration	2 / 29 (6.9%)*
Seroma	1 / 29 (3.4%)*
Confusion	1 / 29 (3.4%)*
Hypotension	1 / 29 (3.4%)*
Incisional Swelling	1 / 29 (3.4%)*
Ileus	1 / 29 (3.4%)*
Ethanol Withdrawal	1 / 29 (3.4%)*

* - Percent of Total Number of patients enrolled in Study.

There was no assessment of immunogenicity in 99-001 study. There were no deaths. The AEs were reviewed and the probability of their relationship to Floseal is very low.

Literature review

In total, 34 publications on Floseal have been provided, which give a comprehensive overview of the use, performance and safety of Floseal in a clinical setting. The total number of patients included in all Floseal publications amounts to about 650. The publications cover following types of surgery: open and laparoscopic partial nephrectomy and nephrolithotomy, endoscopic sinus surgery, vascular surgery, stapled haemorrhoidectomy and rectal prolapse resection, adenoidectomy, acute anterior epistaxis, diaphragmatic injury repair, arterial injury repair after temporomandibular joint replacement, lymphadenectomy, radical prostatectomy, transsphenoidal pituitary surgery, rhinophyma, thyroid surgery, cardiac surgery, spinal surgery.

The reviewed literature included 5 prospective randomized controlled studies and one historically controlled study. One of these studies investigated long-term mucosal healing after endoscopic sinus surgery (Chandra et al., 2005). Hemostasis was evaluated in the other 5 studies and was the primary objective of 4 of these studies:

Type of surgery	**Author, year**	**Number of patients treated with Floseal**	**Design**	**Main results**
Adenoidectomy	Mathiasen and Cruz, 2004	35 (+3 crossed over)	Prospective, randomized, controlled cross-over study (Floseal vs. cautery)	time to hemostasis was significantly shorter (0.6 vs. 9.5 minutes, p<0.001); blood loss was significantly less (2.5 vs. 29.4 mL, p<0.001) in the Floseal group
Epistaxis, acute anterior	Mathiasen and Cruz, 2005	35 (+8 crossed over)	Prospective, randomized, controlled cross-over	Floseal significantly more effective at initial control of epistaxis (p<0.001) as

			study (Floseal vs. nasal packing)	judged by the physicians using a 10-point visual analog scale
Sinus surgery, endoscopic	Baumann and Caversaccio, 2003	50	Prospective, historically controlled study (Floseal vs. polyvinyl acetal sponges)	bleeding was controlled within at least 3 minutes in both groups
Sinus surgery, endoscopic	Chandra et al., 2003	20	Prospective, randomized, controlled study (Floseal vs. thrombin-soaked gelatin foam)	Floseal and control equally effective in averting the need for nasal packing to manage epistaxis after surgery
Sinus surgery, endoscopic	Jameson et al., 2006	at least 23	Prospective, randomized, double-blind, controlled study (Floseal vs. saline soaked neuropatties)	Average time to cessation of bleeding was 16.4 minutes for Floseal and 30.8 minutes for the control (p=0.028)

Postoperative healing complications (increased granulation tissue, adhesion formation) have been reported from one author in patients undergoing endoscopic sinus surgery (Chandra et al., 2003 and Chandra et al., 2005).

Additional safety data

In addition to the safety data from the aforementioned clinical studies, the Applicant has provided safety data from the following sources:

- Post-Marketing experience with Floseal containing Bovine Thrombin

In the period from July 2002 to September 2006 the following medical complaints have been reported (number of cases in parentheses): allergy (6), lack of effect (5), postoperative bleeding (5), embolism (5), neural compression (4). No other type of event was reported more than twice.

- US Post-Marketing experience with Floseal VH

No medical complaints were reported from Floseal VH, the variant including human Thrombin VH, since licensure in the US in March 2005 until the cut-off date of 30 September 2006.

Moreover, the following adverse events have been reported (one case each), but the type of Floseal employed (with bovine or human thrombin) was not specified: inflammation, embolism, infection, pneumoperitoneum, lack of effect and death. For the last event, insufficient data preclude a clear association with the use of the device.

- Human Thrombin Safety Data from Clinical Studies

Human Thrombin VH and human Thrombin VH S/D as used in Floseal VH and Floseal VH S/D were evaluated as ingredients of Fibrin Sealant VH and Fibrin Sealant VH S/D.

- In Clinical Study 550003, the safety of Fibrin Sealant VH S/D compared to Fibrin Sealant VH was evaluated in 317 subjects undergoing cardiac surgery requiring cardiopulmonary bypass and median sternotomy. In this study, no confirmed seroconversions for HAV, HBV, HCV, HIV-1/-2 and B19V for both Fibrin Sealant VH S/D-treated subjects and Fibrin Sealant VH treated subjects were detected. In terms of general safety, no difference was observed between the treatment groups in the number of

subjects with at least one product related AE, in the total number of subjects with at least 1 AE (related or unrelated) and in the types of symptoms reported. No allergic reaction related to any of the 2 fibrin sealants was reported.

- In Clinical Study 550001, in which Fibrin Sealant VH S/D was used in total hip replacement, none of a total of 53 subjects receiving Fibrin Sealant VH S/D had adverse events which were considered to be related to the use of the study product. The symptoms reported were consistent with the type and severity of the surgical intervention and the frequency and severity of these symptoms was similar in the Fibrin Sealant VH S/D treated subjects and in the control subjects who were treated with conventional measures for hemostasis (i.e. sutures, hemostatic clips, cauterization and compression of the bleeding vessels).

- In Clinical Study 550002 investigating the efficacy of Fibrin Sealant VH S/D in the reduction of lymphatic leakage by sealing axillary lymphatics in subjects with breast cancer undergoing lumpectomy and level I and II axillary lymph node dissection, the safety of the product was evaluated in 79 female patients. The frequency and distribution of all AEs reported, related and non-related, was typical for patients with breast cancer undergoing axillary lymph node dissection and lumpectomy. The AE profiles of the subjects in the Fibrin Sealant VH S/D group and in the control group who were treated by conventional surgical methods were similar.

Safety data obtained in these 2 clinical studies, which compared the use of Fibrin Sealant VH S/D as an adjunct to hemostasis (study 550001) and for sealing of axillary lymphatics (study 550002) to conventional methods, showed that there was no difference in terms of type, frequency and severity of the AEs reported between the Fibrin Sealant VH S/D groups and groups on conventional treatment.

- Human Thrombin Safety Data from Market Experience

During the period from 12 November 1991 to 30 November 2005, a total of 296 Adverse Event Reports with Baxter's Fibrin Sealants were received from worldwide reporting sources and documented in Periodic Safety Update Reports. A total of 69 of all AEs reported were assessed as related to fibrin sealant and 44 of these related AEs were serious. The most frequently reported related serious adverse events (SAEs) were allergies including anaphylactic reactions (14 reports) which may at least to some extent be attributable to the bovine aprotinin fibrinolysis inhibitor present in the product, followed by bleeding complications (6 reports) and seromas (5 reports).

No case of potential HIV or hepatitis virus transmission has been documented as related to Baxter's Fibrin Sealants.

- Labelling

The following changes to the Instructions For Use (IFU) were implemented following CHMP recommendations:

- an additional warning to avoid intravascular injection of Floseal

- a further explanation on the warning against application of Floseal in the absence of blood flow, i.e. on clamped or by-passed vessels

- a more stringent warning for invariable removal of excess material

- a precaution to allow 30min between preparation and application of the product to ensure optimal product consistency and performance, in view of the product volume changes occurring during this time that are potentially related to neural compression adverse events

- a revised Adverse Events section including a tabular listing of all adverse events and their frequencies from clinical studies with the predecessor product containing bovine thrombin.

Discussion on Quality, Safety and Usefulness

For manufacture of the final device Floseal VH S/D, the drug product of human Thrombin VH S/D is subjected to primary and secondary packaging. Before administration of the device to the patient human Thrombin VH S/D is reconstituted by the user and mixed with the bovine gelatine. There are no quality issues after human Thrombin VH S/D is incorporated into the medicinal device. The claimed shelf-life for the reconstituted thrombin and of the thrombin solution mixed with the gelatine matrix is supported by stability data.

The non-clinical testing program for Floseal VH S/D was primarily based upon the requirements contained in ISO 10993. A series of non-clinical studies with focus on biocompatibility have been conducted according to the requirements of ISO 10993 using the predecessor product and Floseal VH/SD. The results from testing of Floseal VH/SD and the gelatine component of the predecessor product demonstrate the biocompatibility of Floseal VH/SD according to ISO standards.

The usefulness of the ancillary substance Thrombin VH S/D is contingent upon non-clinical evidence bridging the usefulness of the bovine ancillary substance with that of human Thrombin VH S/D. The comparability of human Thrombin VH S/D to its predecessors has been suggested by the results of pharmacodynamic thromboelastography studies. In addition, the comparable haemostatic efficacy of the human ancillary substance has been demonstrated using the rabbit liver punch model and the liver square model in pigs. Some reservation was expressed concerning the statistical analyses (Fisher test, Wilcoxon test) performed in the pig liver square model. These are flawed from a methodological point of view, since both tests are based on the assumption of independent observations. However, observations within one animal are correlated. In any case, it can be accepted that the results may be interpreted in an explorative manner in support of the superiority claim of Floseal VH S/D versus its comparators (gelatin matrix and thrombin used separately).

Data on reproductive, embryo- and fetal toxicity and carcinogenicity have not been provided and this is acceptable for this type of product. The product is considered to be non-mutagenic and is unlikely to be carcinogenic.

The Applicant has not performed a clinical study with Floseal VH S/D. The bibliographic evidence provided by the applicant in support of the usefulness and clinical performance is for the most part limited to bovine thrombin.

The performance and usefulness of Floseal VH S/D as an adjunct to haemostasis is supported by one clinical study (C98-001) and a second supportive study (C99-001). Both studies employed a predecessor product (Fusion Matrix-WET with bovine thrombin).

The aim of study C98-001 was to show equivalence of the FMW and comparator in controlling intra-operative haemorrhage. However, from a methodological point the aim was not to show equivalence but non-inferiority of FMW vs. comparator (although a definition of non-inferiority is lacking in the study report). With respect to the primary endpoint and the non-inferiority claim the trial was successful as even superiority of FMW over the comparator could be shown. The analysis of the primary efficacy end-point (treatment success in the primary lesion only) provided with border-line statistical significance in favour of Fusion Matrix for vascular and neurosurgery. However, the efficacy comparison based on the evaluation of treatment success considering all lesions is characterised by more robust and statistically significant results. Overall, the efficacy comparison of Fusion Matrix against the comparator (gelfoam+thrombin) is supportive of treatment success in all three surgical specialties. Likewise, for all secondary endpoints, FMW performed better than the control treatment.

The single arm C99-001 study was prematurely terminated after 29 patients had been enrolled, because the device was approved by FDA. The applicant provided a statistical comparison of physicians' perception of the effectiveness of Fusion Matrix WET compared to alternative haemostatic

agents that might have been used, if Fusion Matrix WET had not been available. As the alternative treatments were not applied in this trial, the claimed statistical significance in favour of FMW is based on speculation and not valid from a methodological point of view. Moreover, the suggested potential comparators do not contain any coagulation enhancing factors. However, in view of the positive results of the main study C98-001 using a comparator containing coagulation enhancing factors and considering that the C99-001 study was a supportive trial, it is acceptable that the study supports the findings of the main study.

With respect to safety, data are gained from US market experience of Floseal VH (human thrombin) and clinical data of Thrombin VH (pharmacovigilance, clinical studies) and Thrombin VH S/D (clinical studies) as components of Baxter`s fibrin sealants. There has been no new safety signals identified with Human Thrombin VH S/D. Previously known adverse events with bovine thrombin have included very rare thromboembolic events, immunogenicity risks and neurocompression events (most likely to be related to the volumetric changes in components of device other than ancillary substance itself).

The immunogenic risks related to the use of bovine ancillary substance should have been minimised via switching to the use of human substance. In this respect, the relevance of immunogenicity data of Thrombin VH and Thrombin VH S/D as components of Baxter`s fibrin sealants is somewhat limited because Baxter's Fibrin Sealants contain bovine aprotinin, which is their most immunogenic component and most likely responsible for the majority of allergic reactions to the product.

Human Thrombin VH S/D is undergoing at least two viral inactivation steps to minimise the risk of viral transmission, including the vapour heat and solvent/detergent treatment. The viral safety aspects in relation to human ancillary substance were satisfactorily addressed from studies with Thrombin VH S/D containing fibrin sealants. The post-marketing experience for Floseal use in surgery is extensive and has shown a good safety profile.

The applicant has provided documents of a risk management report, which includes a description of the medical device, categories of potential hazards that could affect product safety, risk analysis, risk evaluation and risk control measures.

All potential risks, risk control measures and evaluation of identified hazards were also presented in a tabulated manner in the supplied risk management report.

According to the overall risk evaluation, the overall risk of the device has been determined to be acceptable. Therefore the reassurance was provided now that the Risk Management Plan for the ancillary substance to the medical device is acceptable.

3.4. Overall conclusions and recommendation

Quality and Safety with regard to transmissible agents

Information on development, manufacture and control of the drug substance and drug product of the ancillary medicinal substance human Thrombin VH S/D were presented in a satisfactory manner. The results of control tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the ancillary medicinal substance should have a satisfactory and uniform performance in the clinic. Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

For manufacture of the final device Floseal, the human Thrombin VH S/D is subjected to primary and secondary packaging only. Before administration of Floseal to the patient Thrombin VH S/D is

reconstituted by the user and mixed with the bovine gelatine. Adequate stability data support the claimed shelf life of the thrombin solution mixed with the bovine gelatine.

Safety

Based on safety data from clinical studies with the predecessor Fusion Matrix Wet containing bovine thrombin, clinical studies with fibrin sealants containing human Thrombin VH and VH S/D and post-marketing experience with Floseal VH and fibrin sealants containing human Thrombin VH and VH S/D, the CHMP concludes that the safety profile of the new Floseal device incorporating human Thrombin VH S/D is similar to the safety profile of the product with human Thrombin VH marketed in the US.

Usefulness

The usefulness of the ancillary substance Thrombin VH S/D has been supported by non-clinical evidence which is confirmative in bridging the usefulness of the bovine ancillary substance with human Thrombin VH S/D. No clinical studies were conducted with Floseal containing the ancillary substance of human nature. However, clinical usefulness evidence has been shown by the two clinical studies with a predecessor device containing the ancillary substance of bovine origin. Based on the positive outcome of pre-clinical bridging studies and positive quality assessment of the ancillary substance, as well as extensive postmarketing experience with both bovine and human products, there is no reason to believe that the usefulness of the human ancillary substance would be inferior to that of bovine Thrombin.

Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality, safety and usefulness of Human Thrombin VH S/D used as ancillary medicinal substance in the Floseal Hemostatic Matrix was favourable and therefore granted a positive opinion in the consultation procedure.