8 August 2012
EMA/CHMP/66309/2012

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: SURGIFLO™ Haemostatic Matrix Kit

Ancillary medicinal substance: Human Thrombin

EMEA/H/D/002301

Applicant: DS Certificering A/S / DGM

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

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# Table of contents

**1. Background information on the procedure ..... 4**
1.1. Submission of the dossier ..... 4
1.2. Steps taken for the assessment of the product ..... 4
1.3. Manufacturers ..... 5
1.4. Remarks to the notified body ..... 5
1.5. Recommended measures to the notified body ..... 5
**2. Scientific overview and discussion ..... 6**
2.1. General information ..... 6
2.2. Quality documentation ..... 7
2.3. Non-clinical documentation ..... 12
2.4. Clinical evaluation ..... 14
2.5. Overall conclusions ..... 28
2.6. Recommendation ..... 28

# Administrative information

| | |
|---|---|
| **Invented name of medical device:** | SURGIFLO™ Haemostatic Matrix Kit |
| **INN (or common name) of the ancillary medicinal substance:** | Human Thrombin |
| **Applicant for medical device CE certification:** | Ferrosan Medical Devices A/S |
| **Notified body:** | DS Certificering A/S / DGM |
| **Applied intended purpose of the device:** | SURGIFLO™ Haemostatic Matrix Kit is indicated for epilesional use in surgical procedures (except ophthalmic) for haemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical. |
| **Intended purpose of the ancillary medicinal substance in the device:** | To provide more rapid and consistent haemostasis than gelatin alone; to support the endogenous clotting process and provide a more stable clot. |
| **Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:** | Powder and solvent for solution<br>800-1200 IU/mL |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The notified body DS Certificering A/S / DGM submitted to the European Medicines Agency (EMA) on 5 February 2010 an application for consultation on human thrombin as ancillary medicinal substance used in the medical device, SURGIFLO™ Haemostatic Matrix Kit, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

## *1.2. Steps taken for the assessment of the product*

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

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

- The application was received by the EMA on 5 February 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first assessment report was circulated to all CHMP members on 16 June 2010. The Co-Rapporteur's first assessment report was circulated to all CHMP members on 2 June 2010.
- During the meeting on 19-22 July 2010, the CHMP agreed on the consolidated list of questions to be sent to the applicant. The final consolidated list of questions was sent to the applicant on 23 July 2010.
- The applicant submitted the responses to the CHMP consolidated list of questions on 13 January 2011.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of questions to all CHMP members on 28 February 2011.
- During the CHMP meeting on 14-17 March 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 18 April 2011.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP members on 3 May 2011.
- During the meeting on 16-19 May 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the committee, issued a positive opinion for the quality and safety including the clinical benefit/risk profile of human thrombin as ancillary medicinal substance(s) used in SURGIFLO™ Haemostatic Matrix Kit on 19 May 2011. General conditions are the use of the ancillary medicinal substance in the medical device.

## *1.3. Manufacturers*

### Manufacturer of the active substance used as ancillary medicinal substance

Omrix biopharmaceuticals Ltd.
MDA Blood Bank
Sheba Hospital
Ramat Gan 52621
POB 888
Kiryat Ono 55000, Israel

An inspection of this manufacturing site was carried out by Irish Medicines Board. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

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

Omrix Biopharmaceuticals /NV
Leonardo Da Vincilaan 15
1831 Diegem, Belgium

### Manufacturer of the medical device

Ferrosan Medical Devices A/S
Sydmarken 5
DK-2860 Soeborg
Denmark
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.

## *1.4. Remarks to the notified body*

None

## *1.5. Recommended measures to the notified body*

As discussed at CHMP, it would be recommended that the notified body request the following from the medical device manufacturer for device approval:

| **Area**[1] | **Description** |
|---|---|
| Quality | **Container Closure Integrity**<br><br>Results for media fill batch N24Z060, put into the closure integrity study of 24 months, are pending. The applicant should notify the competent authorities immediately in case of contamination or leakage. |
| Quality | **Stability of sWFI pre-filled Syringes**<br><br>The proposed shelf-life of 30 months for the sWFI pre-filled syringes when stored at 2°C to 30°C is considered acceptable.<br><br>The applicant is asked to continue the ongoing stability studies and to inform the competent authorities immediately in case of OOS |

| Area[1] | Description |
|---|---|
| | results. |

[1] Areas: quality, safety, including clinical benefit/risk profile.

# 2. Scientific overview and discussion

## *2.1. General information*

This application concerns the initial consultation on lyophilised human thrombin, a plasma-derived ancillary medicinal substance, used in the Class III medical device SURGIFLO™ Haemostatic Matrix Kit submitted to the EMA in accordance with Article 1(4)a of Directive 93/42/EEC as amended by Directive 2007/47/EC.

Directive 2007/47/EC requires that the Notified Body consults and seeks a scientific opinion from the EMA 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.

Here, the Notified Body, DS Certificering A/S DGM, Denmark, is consulting the CHMP regarding the quality and safety including the benefit/risk profile of lyophilised human thrombin, the ancillary substance of SURGIFLO™ Haemostatic Matrix Kit.

The aim of including human thrombin as ancillary substance in SURGIFLO™ Haemostatic Matrix Kit is to enhance the haemostatic effect of SURGIFLO™ Haemostatic gelatin matrix.

Thrombin belongs to the family of Trypsin-like serine proteases which are synthesized as inactive precursors which have to be cleaved during limited proteolysis into the active form. In the manufacture of SURGIFLO™'s human thrombin, Prothrombin is cleaved and released as Thrombin during a chromatographic purification step. Thrombin is a highly specific protease which cleaves e.g., fibrinogen into fibrin.

SURGIFLO™ Haemostatic Matrix Kit is a single use medical device consisting of the following components: 1) porcine-derived SURGIFLO™ Haemostatic Matrix (flowable gelatin matrix), 2) plasma derived lyophilised human thrombin, 3) Needle-free syringe with sWFI (Ph. Eur.) for reconstitution and 4) vial adapter for transfer.

The components are assembled into a kit at Ferrosan Medical Devices A/S being the applicant for CE certification and legal manufacturer of SURGIFLO™ Haemostatic Matrix Kit. Lyophilised human thrombin is supplied in vials containing 2,000 (1,600-2,400) IU thrombin as lyophilised powder. When reconstituted with 2mL of sWFI, the final solution contains 1,000 (800-1,200) IU/mL thrombin.

SURGIFLO™ Haemostatic Matrix and lyophilised human thrombin have to be mixed prior to use.

The accessories required to prepare and apply the two components are supplied within the kit accompanied by appropriate instructions for use. Relevant components have been approved within the CE certification of SURGIFLO™ Haemostatic Matrix.

The intended route of administration for the device is epilesional.

## *2.2. Quality documentation*

### 2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself

In general, the human thrombin drug substance of SURGIFLO™ is identical to that of the Thrombin Component in EVICEL® and Quixil® (medicinal products centrally authorised and via Mutual Recognition Procedure, respectively). However, the thrombin components differ in their pharmaceutical form. Within the medicinal products the Thrombin Component is supplied as a frozen solution, while the SURGIFLO™'s Thrombin Component is presented as a lyophilisate. Further, its composition differs by a small increment in osmolarity, required for optimal lyophilisation and water content.

**Drug substance**

Drug substance of lyophilised human thrombin is identical to that of the Thrombin Component in EVICEL® (Solutions for Sealant Kit), a centrally authorised medicinal product (EMEA/H/C/000898).

*Starting material*

The ancillary substance lyophilised human thrombin is derived from human source plasma collected and tested in FDA-licensed and EU-inspected centres in the USA. Details are provided in Omrix Biopharmaceuticals NV's Plasma Master File, certified centrally by EMA.

*Manufacturer*

The manufacturer of the active substance is Omrix Biopharmaceuticals Ltd., PFI (Plasma Fractionation Institute)

This facility has been inspected by the Irish Medicines Board, and a copy of the current GMP certificate is provided.

*Description of manufacturing process*

The manufacturing process is comprehensively described by the applicant. Briefly, purification of human thrombin comprises adsorption of the prothrombin-complex to anion exchange chromatography resin, generation of thrombin in the eluate in the presence of calcium chloride, and cation exchange chromatography. Steps for virus inactivation and virus removal are included into the manufacturing process.

*Control of materials, Control of critical steps and intermediates*

Control of materials is adequately documented.

The applicant has established in-process-controls and defined acceptance criteria at critical steps of the manufacturing process to assure that the process is controlled. A rationale is given for in-process controls supported by experimental data from human thrombin drug substance batches.

The in-process controls performed during manufacture of human thrombin bulk are appropriate to ensure the quality and consistency of the drug substance.

*Process validation*

Human thrombin validation batches were evaluated for in-process controls, critical process steps, human thrombin release and characterization testing as well as stability studies at real time and accelerated conditions.

The applicant has established appropriate in-process-controls to ensure the quality and consistency of the manufacturing process.

Adequate acceptance criteria at critical steps of the manufacturing process were defined to assure that the process is controlled.

*Manufacturing process development*

The manufacturing development of the drug substance mainly focused on viral safety and purity.

*Characterisation*

The documentation reflects the information as it was provided for the EVICEL® marketing authorisation application and its subsequent variations. The applicant has identified and thoroughly discussed product related as well as process related impurities in human thrombin Drug Substance and provided (where applicable) analysis of their quantitative presence in the bulk and set limits.

*Control of drug substance*

The drug substance specifications are in accordance with the approved specifications for EVICEL®.

The rationale for choice of quality control tests for the drug substance has been presented.

The applicant has established and validated appropriate analytical procedures to control the quality of human thrombin drug substance. Sufficient information has been provided on reference material.

Results of batch analysis are within the limits set and provide evidence that the manufacture of the drug substance is consistent.

*Container closure system*

The drug substance is stored in bags complying with Ph. Eur. monographs.

*Stability*

The design of stability studies is in compliance with ICH guidelines. The stability data presented support the proposed shelf life.

**Drug product**

*Description and composition*

As stated above, the drug substance of lyophilised human thrombin is identical to that of the Thrombin Component in EVICEL®.

However, the drug products of both thrombin components differ in their pharmaceutical form. The thrombin component of EVICEL® and QUIXIL® is a liquid formulation identical in composition to the drug substance; which is essentially sterile filtered and filled. This product is stored at ≤-20°C. The Thrombin Component included as ancillary substance in SURGIFLO™ is supplied as a lyophilisate.

**Composition of Lyophilised Human Thrombin Drug Product**

| **Names of Ingredients** | |
|---|---|
| **Active Substances**<br>Human Thrombin | 800 - 1200 IU/ml |
| **Excipients**<br>Calcium Chloride<br>Human Albumin<br>Mannitol<br>Sodium Chloride*<br>Sodium Acetate<br>Water for Injections | |

*Not part of the CoA

Omrix Biopharmaceuticals NV, Belgium is responsible for final batch release of lyophilised human thrombin Drug Product.

*Manufacture*

The manufacturing process of the drug product is adequately described. The batch formula is given. A flow diagram has been presented. Briefly, processing of the drug substance to drug product includes adjustment of the sodium ion concentration (if required), sterile filtration, aseptic filling and partial stoppering, lyophilisation, vial closure, and over-sealing followed by quality control of batches.

*Process Validation*

The production from Thrombin drug substance to lyophilised human thrombin drug product has been adequately validated. Critical parameters at critical steps of the drug product manufacturing process were identified to assure that the process is controlled to ensure the quality and consistency of the drug product.

*Control of Drug Product*

Adequate specifications were defined for batch release of lyophilised human thrombin drug product and appropriate test methods were established to assure consistent quality of batches. All analytical methods used have been described and validated adequately.

*Batch Analysis*

Batch-to-batch consistency of the validation batches concerning thrombin potency is regarded sufficient. Release data of the lyophilised human thrombin batches were compared to liquid thrombin batches (drug product of EVICEL® manufactured from the same drug substance batches) and to the average results from an annual review. All results complied with the specification.

*Excipients*

All excipients for the pharmaceutical production of lyophilised human thrombin comply with the current edition of the Ph. Eur.

Pasteurized, purified human albumin added during pharmaceutical formulation is used as stabiliser. The only albumin used is Human Albumin 25% and is licensed in some EU member states.

The applicant has provided a separate dossier on the quality of the excipient Human Albumin.

A statement has been provided that only albumin which is within its shelf life is used as excipient in the manufacture of lyophilised human thrombin for SURGIFLO™.

Albumin 25% is purchased by OMRIX biopharmaceuticals as an EU batch-released product and the batch release certificate from Talecris forms part of the batch documentation for Thrombin.

The human albumin is produced from plasma and complies with the Ph. Eur. Monograph "Human Albumin Solution" (0255). The plasma used for fractionation corresponds with the Ph. Eur. Monograph "Human Plasma for Fractionation" (0853).

The required information about sourcing and testing of donations and plasma pools are provided in the PMF . The reference to the PMF is provided in Section "Adventitious Agents Safety Evaluation".

The PMF is approved in line with the approval of the product Albumin.

According to Directive 2003/63/EC a declaration is given that PMF Certificate, Evaluation Report and PMF have been submitted to the applicant by the PMF holder.

*Container Closure System*

The primary packaging for human thrombin lyophilized consists of a glass vial, a rubber stopper and aluminum crimps with plastic caps. Liquid human thrombin is filtered and filled in aliquots into glass vial. Container Closure System presented for lyophilised human thrombin Drug Product is regarded appropriate for its intended use.

Extractables / Leachables Studies on stoppers were performed. Risk assessment by a consultant toxicologist reveals that those chemicals identified to be leached under extreme conditions to low levels are unlikely to pose a health risk to the patient.

The extraction study has been repeated with the lyophilised product.

*Closure Integrity*

The container closure integrity system has been adequately validated. With the response document to Day 180 list of outstanding issues the results of three media fill batches have been provided demonstrating that the closure system integrity is validated for the use of the vials and the rubber stoppers. Results for the fourth batch were pending at the time of CHMP opinion.

**Stability**

The proposed shelf life of 24 months for lyophilized thrombin drug product when stored at 2-25°C is sufficiently supported by stability data and is acceptable. Real-time stability data for 24 months have

been provided along with a statistical analysis. Values obtained for the parameters analysed comply with the specification. The proposed holding time of 8 hours of the reconstituted product at room temperature is sufficiently supported by stability data as well and is acceptable.

**Solvent (sterile Water for Injection (sWFI) in a pre-filled syringe)**

sWFI is a kit component and part of the ancillary medicinal product, as it is used for its reconstitution. The full quality dossier in relation to the manufacture and control of the sWFI product was provided for assessment.

The solvent is sWFI supplied in a pre-filled syringe (glass; Ph.Eur.). The sWFI pre-filled syringes are manufactured and tested for compliance with the appropriate specifications. Copies of the Manufacturing License, as well as copies of GMP certificates for the facilities involved in the manufacture of sWFI pre-filled syringes have been submitted.

The applicant has provided a separate dossier on the manufacturing process, its validation and quality control of the sWFI pre-filled syringes documenting adequately the quality of the sWFI pre-filled syringes. Process validation included identification of critical steps. In-process controls have been established ensuring consistent and reproducible processing of the product. The specifications and methods for testing sWFI pre-filled syringes comply with Ph. Eur.

The proposed shelf-life of 30 months for the sWFI pre-filled syringes when stored at 2°C to 30°C is considered acceptable based on the provided stability data. The applicant is asked to inform the competent authorities immediately in case of out-of-specification (OOS) results. Based on the data reviewed sWFI pre-filled syringes are considered to be suitable for their use as solvent of lyophilised human thrombin, the ancillary substance in SURGIFLO™ Haemostatic Matrix kit.

**Adventitious agents' safety**

The Thrombin component of SURGIFLO™ is produced from human plasma. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations. Single donations are screened by an adequate testing program for viral infections (Anti HIV, HBsAg, Anti-HCV). Further nucleic acid amplification tests are performed on minipools with regard to HIV, HBV, HCV, HAV, and parvovirus B19. Manufacturing pools are tested by NAT HCV-RNA. Donors with an increased risk for sporadic or variant Creutzfelt-Jakob-Disease are excluded. The donor selection and plasma donation testing strategy for viral markers is considered adequate.

The virus reduction strategy for thrombin is based on an efficient inactivation step for enveloped viruses and a virus filtration step which has been demonstrated to remove enveloped viruses as well as small non-enveloped viruses such as parvoviruses.

Plasma is sourced from adequately-selected and tested donors. Plasma pools for albumin are tested according to the regulations. The viral risk from albumin has been adequately minimised.

A warning in the Instructions for Use has been amended to include additional wording regarding adventitious agents in analogy to 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)**:**

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

With the response to the Day 180 list of outstanding issues the applicant implemented the following statement in the Instructions for Use as requested: "Tracking labels are provided in the kit to record name and batch number of the product to link use to the patient record. It is strongly recommended that every time that SURGIFLO™ Haemostatic Matrix is administered to a patient, the name and batch number of the product is recorded in order to maintain a link between the patient and the batch of the product."

**Discussion and conclusion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the drug substance and drug product of the ancillary medicinal substance, lyophilised 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.

## 2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

**General Information**

General remark: The extent of the information submitted is in accordance with Meddev 2.1/3 rev 3.

Sufficient justification for the inclusion of the ancillary medicinal substance in the medical device has been provided; and full descriptions of the kit components are included (see 2.1).

**Quality Documentation**

Since the human thrombin will be mixed with the SURGIFLO™ Haemostatic matrix (porcine-derived gelatin) immediately before use, quality considerations for the ancillary substance described in the section above "Ancillary medicinal substance **before** incorporation in the medical device" will also apply here.

## *2.3. Non-clinical documentation*

**Pharmacodynamics**

The non-clinical documentation submitted for this consultation procedure comprised several non-clinical studies conducted either to support the current consultation procedure by investigating the components of SURGIFLO™ Haemostatic Matrix kit or in preparation of marketing authorisation applications for other fibrin sealants containing human thrombin.

Two studies were submitted which aimed to investigate the haemostatic efficacy of the SURGIFLO™ Haemostatic Matrix in combination with human thrombin (liquid frozen) or without it.

The purpose of one submitted study was to evaluate the haemostatic efficacy of SURGIFLO™ Haemostatic Matrix plus Thrombin compared to SURGIFLO™ Haemostatic Matrix plus saline or compared to Thrombin alone by using a porcine spleen model. The three treatment groups were compared by evaluating the haemostatic efficacy measured as time to haemostasis (TTH) in freely bleeding, linear incisions on porcine spleen. SURGIFLO™ with thrombin demonstrated the fastest time to haemostasis (median 145sec), followed by SURGIFLO™ with Saline (median 282.5sec). Moreover,

thrombin alone was not able to achieve haemostasis within 12 minutes (Median >720sec) in the absence of a carrier (haemostatic matrix) to deliver it to the wound site.

The purpose of another submitted study was to compare the haemostatic properties of SURGIFLO™ Haemostatic Matrix when mixed with 2000 IU Thrombin, with 5000 IU Thrombin, and with 5ml Saline control by using a porcine punch biopsy spleen model. The primary endpoint was percentage of haemostasis within 2 minutes.

The following results were obtained:

| **SURGIFLO +** | **Haemostasis <2 MIN** | **Haemostasis <4 MIN** |
|---|---|---|
| 5 ml Thrombin | 96% | 100 % |
| 2 ml Thrombin | 88% | 100% |
| 5 ml Saline | 0% | 88% |

The study indicated that SURGIFLO™ combined with either 5 or 2 ml Thrombin achieved comparable results and was more effective within 2 minutes than the SURGIFLO™ plus saline control. Differences were statistically significant. On the other hand, all groups displayed similar efficacy and had no statistical significant differences in their haemostatic properties within 4 minutes.

Moreover, a study comparing the efficacy of lyophilised and reconstituted thrombin with that of liquid frozen thrombin, was submitted. This comparability study employed the porcine bleeding spleen model and its primary endpoint was Time to Haemostasis (in seconds) of the two types of thrombin given in combination with an absorbable gelatin sponge. Sponge soaked in saline served as control of the haemostatic efficacy of the sponge itself and gauze served as negative control.

The following results were obtained:

| Group | Vehicle | Replicates | Treatment | Avg. TTH±SD (sec) |
|---|---|---|---|---|
| A | Sponge | 24 | Liquid Thrombin | **50±19** |
| B | Sponge | 24 | Lyophilized Thrombin | **46±18** |
| C | Sponge | 24 | Saline (Sponge effect) | **91±79** |
| Gauze | Gauze | 2 | None | **>600*** |

* The gauze control failed to achieve haemostasis even after 10 minutes of compression

**Pharmacokinetics**

No studies with SURGIFLO™ Haemostatic Matrix and lyophilised human thrombin were submitted. Instead, absorption following spray application of human thrombin alone was investigated in two studies by using a rabbit partial hepatectomy model (see discussion on the non-clinical documentation).

**Toxicity**

No specific toxicology studies for human thrombin in the context of its use within the SURGIFLO™ Haemostatic Matrix kit were submitted. Instead, the Applicant made reference to toxicity and biocompatibility testing separately for the components of this product, namely SURGIFLO™ Haemostatic Matrix, human thrombin, sterile Water for Injection and vial adapter (see discussion on the non-clinical documentation).

**Local tolerance**

Similarly to toxicity testing above, reference was made to local tolerance testing performed separately for each of the components of the medical device (see discussion on the non-clinical documentation).

### 2.3.1. Discussion and conclusion on the non-clinical documentation

The non-clinical information submitted within this consultation procedure is mainly based on studies aimed to support marketing authorisation applications for other fibrin sealants containing thrombin. Two pharmacodynamic studies have been conducted to demonstrate the ancillary function of thrombin when mixed with SURGIFLO™ Haemostatic Matrix. Some methodological limitations in one of these studies were pointed out. In one study, only two animals were investigated (one animal served for testing the Flowable Gelatin Matrix with saline, the other was tested for haemostatic properties of the Flowable Gelatin Matrix with thrombin and thrombin alone). Furthermore, the testing on the two animals was performed on different days.

A comparability study was submitted supporting the equivalence in haemostatic efficacy and safety of liquid (maintained frozen) thrombin and lyophilised (and reconstituted with sterile water for injection prior to use) thrombin. These are considered important bridging data, as with both non-clinical and clinical documentation the applicant submitted only studies in which liquid thrombin was used. Extrapolation about the efficacy and safety of the lyophilized thrombin employed in the SURGIFLO™ Haemostatic Matrix kit can be made on the basis of these bridging data.

Regarding pharmacokinetics, it was agreed that the PK of thrombin when mixed with the Flowable Gelatin Matrix prior to placing at the surgical site is not different from the well-known PK of thrombin used alone or from the PK of endogenous thrombin. The absence of specific toxicity and local tolerance data on the use of thrombin in the context of the medical device was also considered acceptable considering the low toxicity and acceptable local tolerance/low tissue reactivity of each of the components of the device used separately.

Since the pharmacological and toxicological profile of thrombin is well understood and no new information would be expected from further animal studies, the non-clinical data submitted were considered sufficient for the purposes of the consultation procedure.

## *2.4. Clinical evaluation*

### 2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body

No clinical studies with human thrombin incorporated in the SURGIFLO™ Haemostatic Matrix kit were submitted. Efficacy and safety data to support the usefulness of human thrombin incorporated in the SURGIFLO™ Haemostatic matrix kit were derived from 1) a clinical study conducted using SURGIFOAM® with human thrombin and 2) a literature review. Additional safety data of the combination of human thrombin with fibrin sealants (with or without tranexamic acid) are available from the clinical development of EVICEL® and QUIXIL® as well as from post-marketing experience with EVICEL®, QUIXIL® and EVITHROM® (human thrombin used as medicinal product in the USA).

**Clinical Study**

This was a Phase III (pivotal), multicenter, prospective, randomised, controlled, double-blind study comparing Thrombin, Topical (Human) to Thrombin, Topical (Bovine) in achieving intraoperative haemostasis during cardiovascular, neurologic (spine), and general surgery. The bovine thrombin and human thrombin were applied topically via SURGIFOAM® Absorbable Gelatin Sponge, U.S.P., an absorbable gelatin sponge.

The primary objective of this study was to demonstrate that the safety and efficacy of human thrombin (Omrix) is equivalent to that of bovine thrombin (Thrombin-JMI®). The primary endpoint of the study was success in achieving haemostasis within 10 minutes of product application during surgery. The secondary endpoints of this study were the success in haemostasis at 3 minutes and 6 minutes post-product application.

In total, 305 patients (153 treated with human thrombin, 152 treated with bovine thrombin) were randomised into this study. A total of 93 patients underwent cardiovascular surgery, 121 patients underwent neurologic (spine) procedures, and 91 patients underwent general surgery or posttraumatic procedures.

The results in the Intent-to-Treat population in terms of the primary and the two secondary efficacy endpoints are shown in the following tables.

**Table: Proportion of patients achieving haemostasis within 10 mins of application**

| Surgical Specialty | Treatment Group: % (#Successes/N) | | Ratio Human/Bovine | 95% CI for Ratio Human/Bovine[1,2] |
|---|---|---|---|---|
| | Human Thrombin | Bovine Thrombin | | |
| Cardiovascular | 95.74 (45/47) | 91.30 (42/46) | 1.05 | (0.93, 1.21) |
| Neurologic (Spine) | 100.00 (61/61) | 100.00 (60/60) | 1.00 | (0.94, 1.06) |
| General Surgery | 95.56 (43/45) | 100.00 (46/46) | 0.96 | (0.85, 1.04) |
| Overall | 97.39 (149/153) | 97.37 (148/152) | 1.00 | (0.96, 1.05) |

[1] 95% CI is for the ratio of proportions of success

[2] For the 2 treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

**Table: Proportion of patients achieving haemostasis within 6 mins of application**

| Surgical Specialty | Treatment Group: % (#Successes/N) | | Ratio Human/Bovine | 95% CI for Ratio Human/Bovine[1,2] |
|---|---|---|---|---|
| | Human Thrombin | Bovine Thrombin | | |
| Cardiovascular | 93.62 (44/47) | 82.61 (38/46) | 1.13 | (0.97, 1.36) |
| Neurologic (Spine) | 98.36 (60/61) | 98.33 (59/60) | 1.00 | (0.93, 1.08) |
| General Surgery | 91.11 (41/45) | 95.65 (44/46) | 0.95 | (0.82, 1.08) |
| Overall | 94.77 (145/153) | 92.76 (141/152) | 1.02 | (0.96, 1.09) |

[1] 95% CI is for the ratio of proportions of success

[2] For the 2 treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

**Table: Proportion of patients achieving haemostasis within 3 mins of application**

| Surgical Specialty | Treatment Group: % (#Successes/N) | | Ratio Human/Bovine | 95% CI for Ratio Human/Bovine[1,2] |
|---|---|---|---|---|
| | Human Thrombin | Bovine Thrombin | | |
| Cardiovascular | 61.70 (29/47) | 63.04 (29/46) | 0.98 | (0.71, 1.35) |
| Neurologic (Spine) | 83.61 (51/61) | 80.00 (48/60) | 1.05 | (0.88, 1.25) |
| General Surgery | 71.11 (32/45) | 71.74 (33/46) | 0.99 | (0.75, 1.30) |
| Overall | 73.20 (112/153) | 72.37 (110/152) | 1.01 | (0.88, 1.16) |

[1] 95% CI is for the ratio of proportions of success

[2] For the 2 treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

Equivalence of human thrombin to bovine thrombin was shown in achieving haemostasis within 10 minutes in mild to moderate bleeding that was not amenable to standard techniques. Overall, the human thrombin and bovine thrombin treatments were equivalent based on the proportions of patients who achieved haemostasis within 10 minutes (97% in each group), 6, and 3 minutes of product application. The two preparations also performed similarly within surgical specialties.

Safety assessments included monitoring and recording of adverse events up to 5 weeks (±7 days) following surgery; laboratory tests (complete blood count and white cell differential) within 12 hours of surgery and within 24 hours of discharge from the hospital.

**Table: Summary of adverse events**

| Type of Adverse Event | Thrombin Type | | Total |
|---|---|---|---|
| | Human (n=153) | Bovine (n=152) | (n=305) |
| Subjects with at least 1 AE in the following categories: | | | |
| Any adverse event | 152 (99.4%) | 152 (100.0%) | 304 (99. 7%) |
| Serious adverse event | 26 (17.0%) | 17 (11.2%) | 43 (14.1%) |
| Serious related[1] adverse event | 2 (1.3%) | 2 (1.3%) | 4 (1.3%) |
| Related[1] adverse event | 19 (12.4%) | 18 (11.8%) | 37 (12.1%) |
| Severe adverse event | 21 (13.7%) | 15 (9.9%) | 36 (11.8%) |
| Severe related[1] adverse event | 1 (0.7%) | 1 (0.7%) | 2 (0.7%) |
| | | | |
| **Number of Actual Events (not subjects); Percentages Based on Total Number of Adverse Events:** | | | |
| Total Number of AEs[2] | **1,712** | **1,692** | **3,404** |
| Serious adverse events[2] | 50 (2.9%) | 31 (1.8%) | 81 (2.4%) |
| Relationship to treatment with study drug | | | |
| Not related | 1,674 (97.8%) | 1,642 (97.0%) | 3,316 (97.4%) |
| Possibly related | 38 (2.2%) | 49 (2.9%) | 87 (2.6%) |
| Probably related | 0 | 1 (0.1%) | 1 (0.0%) |
| Intensity of adverse[2] | | | |
| Mild | 1,269 (74.1%) | 1,283 (75.8%) | 2,552 (75.0%) |
| Moderate | 392 (22.9%) | 382 (22.6%) | 774 (22.7%) |
| Severe | 51 (3.0%) | 27 (1.6%) | 78 (2.3%) |
| Action taken for adverse event[2] | | | |
| None | 1,004 (58.8%)[3] | 1,018 (60.2%) | 2,022 (59.5%)[4] |
| Medical | 639 (37.4%)[3] | 604 (35.7%) | 1243 (36.6%)[4] |
| Surgical | 30 (1.8%)[3] | 13 (0.8%) | 43 (1.3%)[4] |
| Other | 36 (2.1%)[3] | 57 (3.4%) | 93 (2.7%)[4] |
| Outcome[2] | | | |
| Resolved with treatment | 567 (33.1%) | 519 (30.7%) | 1,086 (31.9%) |
| Resolved spontaneously | 427 (24.9%) | 440 (26.0%) | 867 (25.5%) |
| Ongoing at end of study | 718 (41.9%) | 733 (43.3%) | 1451 (42.6%) |

[1]Related=possibly, probably, or definitely related to study drug.
[2]Regardless of relationship to treatment with study drug.
[3]Percentages based on a total number of 1709 adverse events (instead of 1712) because definitive actions were not reported for 3 adverse events reported for subjects treated with human thrombin.
[4]Percentages based on a total number of 3401 adverse events (instead of 3404), accounting for the 3 adverse events for which no definitive actions were reported.

Most adverse events reported in this study were typical for these patient populations. The majority were mild in intensity, required no action (medical or surgical), and were considered by the investigator as not related to treatment with study drug. The adverse events profiles in both treatment groups were similar, with laboratory abnormalities being the predominant adverse events.

The most common adverse events in both groups included decreased lymphocytes, haematocrit, RBCs, and haemoglobin; and increased neutrophils and WBC. All of these most common adverse events are typical findings in post-operative populations. The most common non-laboratory adverse event in both groups was nausea.

No clinically significant differences were noted in age (≤65 years, >65 years) or gender subgroup analyses of adverse events between treatment groups. Few adverse events differed in incidence between the groups by more than 10% and were mostly laboratory abnormalities which resolved within 24 hours prior to discharge.

**Table: Incidence of adverse events reported in at least 10% of patients**

| System Organ Class/Adverse Event | Thrombin Type | | Total |
|---|---|---|---|
| | Human (n=153) | Bovine (n=152) | (n=305) |
| **Investigations** | **146 (95.4%)** | **149 (98.0%)** | **295 (96.7%)** |
| Lymphocyte count decreased | 89 (58.2%) | 88 (57.9%) | 177 (58.0%) |
| Neutrophils increased | 84 (54.9%) | 80 (52.6%) | 164 (53.8%) |
| Hematocrit decreased | 80 (52.3%) | 89 (58.6%) | 169 (55.4%) |
| Red blood cell count decreased | 79 (51.6%) | 86 (56.6%) | 165 (54.1%) |
| Hemoglobin decreased | 77 (50.3%) | 86 (56.6%) | 163 (53.4%) |
| White blood cell count increased | 68 (44.4%) | 73 (48.0%) | 141 (46.2%) |
| Prothrombin time prolonged | 59 (38.6%) | 62 (40.8%) | 121 (39.7%) |
| Activated partial thromboplastin time prolonged | 39 (25.5%) | 46 (30.3%) | 85 (27.9%) |
| International normalized ratio increased | 32 (20.9%) | 29 (19.1%) | 61 (20.0%) |
| Platelet count decreased | 28 (18.3%) | 32 (21.1%) | 60 (19.7%) |
| Monocyte count increased | 20 (13.1%) | 25 (16.4%) | 45 (14.8%) |
| Lymphocyte percentage decreased | 18 (11.8%) | 18 (11.8%) | 36 (11.8%) |
| Mean cell hemoglobin concentration decreased | 18 (11.8%) | 22 (14.5%) | 40 (13.1%) |
| Monocyte count decreased | 18 (11.8%) | 16 (10.5%) | 34 (11.1%) |
| Neutrophil percentage increased | 16 (10.5%) | 13 (8.6%) | 29 (9.5%) |
| | | | |
| **Gastrointestinal Disorders** | **85 (55.6%)** | **84 (55.3%)** | **169 (55.4%)** |
| Nausea | 63 (41.2%) | 48 (31.6%) | 111 (36.4%) |
| Constipation | 38 (24.8%) | 37 (24.3%) | 75 (24.6%) |
| | | | |
| **Blood and Lymphatic System Disorders** | **39 (25.5%)** | **28 (18.4%)** | **67 (22.0%)** |
| Anemia | 31 (20.3%) | 24 (15.8%) | 55 (18.0%) |
| | | | |
| **General Disorders and Administration Site Conditions** | **52 (34.0%)** | **48 (31.6%)** | **100 (32.8%)** |
| Pyrexia | 27 (17.6%) | 27 (17.8%) | 54 (17.7%) |
| Pain | 16 (10.5%) | 15 (9.9%) | 31 (10.2%) |
| | | | |
| **Nervous System Disorders** | **42 (27.5%)** | **58 (38.2%)** | **100 (32.8%)** |
| Insomnia | 24 (15.7%) | 26 (17.1%) | 50 (16.4%) |
| | | | |
| **Musculoskeletal and Connective Tissue Disorders** | **36 (23.5%)** | **29 (19.1%)** | **65 (21.3%)** |
| Back pain | 22 (14.4%) | 17 (11.2%) | 39 (12.8%) |
| | | | |
| **Metabolism and Nutrition Disorders** | **46 (30.1%)** | **48 (31.6%)** | **94 (30.8%)** |
| Hypomagnesemia | 21 (13.7%) | 17 (11.2%) | 38 (12.5%) |
| Hypokalemia | 18 (11.8%) | 18 (11.8%) | 36 (11.8%) |
| Hypophosphatemia | 16 (10.5%) | 17 (11.2%) | 33 (10.8%) |
| | | | |
| **Injury, Poisoning, and Procedural Complications** | **50 (32.7%)** | **55 (36.2%)** | **105 (34.4%)** |
| Post-procedural pain | 20 (13.1%) | 17 (11.2%) | 37 (12.1%) |
| Incision site complication | 13 (8.5%) | 21 (13.8%) | 34 (11.1%) |

Most of the reported SAEs were typical for these populations and not considered to be related (possibly, probably, or definitely) to treatment with study drug. A majority of the SAEs were associated with post-surgical complications or the patient's overall medical condition. The SAEs reported most often were wound infection and post-procedural complication, each reported in 5/305 (2%) patients: 3/153 (2%) patients treated with human thrombin and 2/152 (1%) patients treated with bovine thrombin. No other SAE was reported in more than 2 patients treated with either human or bovine thrombin.

SAEs considered related to study drug by the investigator were experienced in 2/153 (1.3%) patients receiving human thrombin: Patient 27012 (respiratory arrest and post-procedural hematoma) and Patient 33003 (extradural hematoma). Among bovine thrombin-treated patients, SAEs considered

related to study drug by the investigator were experienced in 2/152 (1.3%) patients: Patient 16001 (pyrexia) and Patient 41007 (post-procedural hematoma). There was no difference seen in the proportion of patients experiencing SAEs related to study drug between the 2 treatment groups.

No patient died during the study period. One patient died post study; a 71-year-old male treated with bovine thrombin, died due to sepsis 3 months after his surgery, approximately 1 month after completing the study.

**Table: Incidence of patients with related adverse events reported in at least 1% of patients**

| System Organ Class/Adverse Event | Thrombin Type | | Total (n=305) |
|---|---|---|---|
| | Human (n=153) | Bovine (n=152) | |
| **Investigations** | **11 (7.2%)** | **14 (9.2%)** | **25 (8.2%)** |
| Activated partial thromboplastin time increased | 4 (2.6%) | 8 (5.3%) | 12 (3.9%) |
| International normalized ratio increased | 4 (2.6%) | 5 (3.3%) | 9 (3.0%) |
| Lymphocyte count decreased | 4 (2.6%) | 2 (1.3%) | 6 (2.0%) |
| Prothrombin time prolonged | 4 (2.6%) | 8 (5.3%) | 12 (3.9%) |
| Neutrophil count increased | 3 (2.0%) | 2 (1.3%) | 5 (1.6%) |
| Platelet count decreased | 1 (0.7%) | 2 (1.3%) | 3 (1.0%) |
| White blood cell count increased | 1 (0.7%) | 2 (1.3%) | 3 (1.0%) |
| Platelet count increased | 0 | 2 (1.3%) | 2 (0.7%) |
| | | | |
| **Vascular Disorders** | **2 (1.3%)** | **2 (1.3%)** | **4 (1.3%)** |
| Hypotension | 2 (1.3%) | 1 (0.7%) | 3 (1.0%) |
| | | | |
| **Skin and Subcutaneous Tissue Disorders** | **1 (0.7%)** | **3 (2.0%)** | **4 (1.3%)** |
| Pruritis | 1 (0.7%) | 3 (2.0%) | 4 (1.3%) |
| | | | |
| **General Disorders and Administration Site Conditions** | **0** | **3 (2.0%)** | **3 (1.0%)** |
| Pyrexia | 0 | 2 (1.3%) | 2 (0.7%) |

Evaluation of mean baseline values versus mean values at 12 hours post-operatively and within 24 hours of discharge for complete blood count and white blood cell differential assessments revealed no unexpected results. Mean laboratory values for human thrombin-treated patients and bovine thrombin-treated patients showed similar changes from the pre-operative to post-operative time points.

*Antibody Response to Thrombin in Clinical Study*

As part of the safety and efficacy study of Thrombin, Topical (Human) versus Thrombin, Topical (Bovine), serum samples were collected and analyzed. Seroconversion rates for each of the antibodies were compared between treatment groups.

*Antibody Response and Seroconversion Patterns*

Patients in the bovine thrombin treated group seroconverted for at least one of the antibodies more frequently than those in the human thrombin treated group (12.70% versus 3.28%, CI of ratio 0.09-0.71, p = 0.01). In the bovine treated group, 11.90% of patients developed antibodies to bovine thrombin or bovine Factor V/Va and in the human treated group, 0.0% developed antibodies to human thrombin or human Factor V/Va. Evaluation of seroconversion frequencies for the individual antibodies revealed a consistent pattern of higher seroconversion rates in the bovine treated group than in the human treated group; anti-bovine thrombin (7.94% versus 2.46%, CI of ratio 0.09-1.01, p = 0.053), anti-bovine Factor V/Va (9.52% versus 1.64%, CI of ratio 0.04-0.67, p = 0.01), and anti-human thrombin (2.38% versus 0.00%, CI of ratio 0.00-1.30, p = 0.09).

No patient in either group was determined to have had seroconversion for anti-human Factor V/Va antibodies. These observations strongly support the hypothesis that the human thrombin is less immunogenic than the comparator, bovine thrombin.

*Patients Who Presented with Pre-existing Antibodies*

In the human thrombin treated group, 12 patients presented at screening with elevated antibody titers to at least one of the four assayed antigens. Following treatment with human thrombin, none of these twelve patients developed seroconversion for any antibody tested. Of special interest, 3 of these 12 patients presented with elevated antibodies to human thrombin at screening but did not seroconvert for any of the antibodies following treatment with human thrombin.

In the bovine treated group, 4 patients presented at screening with elevated antibodies to at least one of the assayed antigens. One (25%) of these patients (15011), who presented with an elevated titer for antibovine thrombin antibodies, developed high titer seroconversion for antibovine thrombin, antibovine Factor V, and for antihuman thrombin after treatment with bovine thrombin. This observation is similar to those of previous reports, noting that patients presenting with pre-existing anti-bovine thrombin antibodies can have a strong immunological response to exposure to bovine thrombin. These comparative findings also support the hypothesis that human thrombin, is less immunogenic than bovine thrombin.

There were four patients in the human thrombin treated group who seroconverted for anti-bovine thrombin and/or anti-bovine Factor V/Va. One of these patients had been exposed to bovine thrombin one year prior to enrollment in the current study and after exposure to human thrombin seroconverted for anti-bovine thrombin and anti-bovine Factor V/Va. Considering the known similarity in peptide sequence between the bovine and human thrombin proteins, it is conceivable that the administration of human thrombin to this previously bovine thrombin-sensitized patient elicited a "booster-like" effect on the background of immune memory. Another of these 4 patients was exposed to commercial bovine thrombin after the screening sample had been drawn but before enrollment in the study (not a protocol violation). It is not known whether this patient's seroconversion for anti-bovine Factor V/Va was related to the exposure to commercial bovine thrombin or to human thrombin.

**Literature review**

The basis for the literature review was a search of PubMed for relevant search terms (such as haemostatic matrix, gelatin haemostat, thrombin, etc.).

***Efficacy***

The mechanism of action of the gelatin haemostatic Flowable Gelatin Matrix is to initiate clotting through the physical contact activation of platelets, leading to platelet aggregation, degranulation, and activation of endogenous clotting factors (Davie and Kulman 2006, Gabay 2006, Lawson 2006, Martinowitz and Saltz 1996, Porte and Leebeek 2002, Traver and Assimos 2006). Endogenous thrombin promotes haemostasis by converting fibrinogen to fibrin, which then becomes a cross-linked fibrin clot. Various other factors are also activated by thrombin (e.g., Factor XIII to Factor XIIIa), thus potentiating the haemostatic effect (Davie and Kulman 2006).

By promoting haemostasis, thrombin contributes to the control of bleeding which is the intended purpose of haemostatic matrices. Control of bleeding during surgery is critical to both surgeon and patient, as it prevents patient morbidity and improves recovery and it also enhances the surgical process by increasing visibility in the surgical field. Control of bleeding has been evaluated in clinical studies using various endpoints and results per endpoint are presented in the following.

*TTH - Absolute Time to Haemostasis*

TTH is an accepted measure of haemostatic effectiveness for haemostatic products (Silverman et al. 2005). The efficacy of a flowable formulation of gelatin + thrombin was studied in a series of three published prospective, multi-center, randomized, controlled clinical studies comparing flowable gelatin (bovine) + thrombin (bovine) with gelatin sponge + thrombin (bovine) (Oz et al. 2000, Renkens et al. 2001, Weaver et al. 2002). These studies were similar in design and differed in the type of surgery that was conducted (cardiovascular, spinal and vascular, respectively).

Median TTH at the first bleeding site is shown in Table 1 below. The TTH was statistically significantly shorter in the flowable gelatin + thrombin group compared to the gelatin sponge + thrombin group. This same relationship was observed in all bleeding sites treated, p<0.001 in all three studies.

| | **MEDIAN TTH FLOWABLE GELATIN + THROMBIN** | **MEDIAN TTH GELATIN SPONGE + THROMBIN** | **P value** |
|---|---|---|---|
| Oz et al. 2000<br>Cardiac Surgery | Median not provided<br>[Statistically signif. shorter than comparison group] | Median not provided | ≤0.001 |
| Renkens et al. 2001<br>Spinal surgery | 1.5 min<br>[95% CI 1 – 1.5] | 3.0 min<br>[95% CI 2 – 4.5] | <0.001 |
| Weaver et al. 2002<br>Vascular surgery | 2.5 min<br>[95% CI 2 – 4] | 6.5 min<br>[95% CI 4.5 – 8] | = 0.001 |

Bleeding during or after adenoidectomy surgery in children is a significant clinical concern to pediatric surgeons. Although the product literature contains a warning that the safety of SURGIFLO™ Haemostatic Matrix use in children is not established, in one published study (Mathiasen and Cruz 2004) Flowable gelatin + Thrombin (bovine, n=35) was compared to cautery (n=35) in a prospective, randomized, single-blind clinical study in children having adenoidectomy surgery. In this study, GEL+THR patients had statistically significantly shorter TTH than cautery patients (0.6 ± 1.3 min vs. 9.5 ± 5.4 min, respectively, p<0.001) and statistically lower blood loss and easier surgical procedure because of haemostasis (discussed below). The efficacy of flowable gelatin was also suggested by the fact that three patients in the cautery group were switched to the flowable gelatin + thrombin group (per-protocol), as the blood loss was difficult to control.

Control of intraoperative bleeding was reported in a retrospective case-series of seven patients with refractory neurological bleeding during cranial surgery who were treated with flowable gelatin-thrombin matrix (Fiss et al. 2007). The patients had various surgical issues, but excessive bleeding in all patients was stopped within 4 minutes of flowable gelatin application (2/7 patients required additional techniques).

In a study using gelatin sponge, the benefit of adding thrombin was shown. In this case, thrombin was shown to improve TTH in a randomized, controlled, double-blind Phase 2 clinical study comparing gelatin sponge + thrombin (recombinant human) (n=64) to gelatin sponge + placebo (n=66, Chapman et al. 2006). TTH hazard ratio was 1.3 favouring the Gelatin sponge + thrombin group.

*Proportion of Success in Achieving Haemostasis within 10 Minutes*

The proportion of success in achieving haemostasis within 10 minutes is often used as a primary efficacy outcome measure in haemostasis studies.

The series of clinical studies mentioned above (efficacy of flowable gelatin + thrombin vs. gelatin sponge + thrombin; Oz et al. 2000, Renkens et al. 2001, Weaver et al. 2002) measured the proportion of success in achieving haemostasis within 10 minutes at the first treated bleeding site and at all treated bleeding sites. In all three studies, the efficacy of the flowable gelatin matrix + thrombin was

higher than that of gelatin sponge + thrombin in achieving haemostasis at 10 minutes at both the first treated bleeding site and all bleeding sites (see Table 2 below).

| | % HAEMOSTASIS FLOWABLE GELATIN + THROMBIN | % HAEMOSTASIS GELATIN SPONGE + THROMBIN | P value |
|---|---|---|---|
| **FIRST BLEEDING SITE** | | | |
| Oz et al. 2000 | 45/48, 94% | 27/45, 60% | 0.001 |
| Renkens et al. 2001 | 64/65, 98% | 56/62, 90% | 0.042 |
| Weaver et al. 2002 | 40/43, 93% | 35/46, 76% | 0.036 |
| **ALL BLEEDING SITES TREATED** | | | |
| Oz et al. 2000 | 92/104, 88% | 35/61, 57% | <0.001 |
| Renkens et al. 2001 | 179/180, 99% | 158/170, 93% | 0.001 |
| Weaver et al. 2002 | 86/93, 92% | 73/92, 79% | 0.010 |

Haemostasis within 10 minutes in the 95% range was reported for gelatin sponge with thrombin (both bovine and human origin, Chapman et al. 2007, Nasso et al. 2009, Woodworth et al. 2009). In an unpublished clinical study conducted with EVITHROM®(human thrombin), 97% haemostasis was achieved in 10 minutes for patients treated with gelatin sponge with Thrombin (both bovine and human origin). In these studies, there was no non-thrombin group for comparison.

*Need for Rescue Therapy*

In a study of various surgical procedures including arteriovenous graft, major hepatic resection, peripheral arterial bypass surgery, and spinal surgery, the efficacy of gelatin sponge + thrombin vs. sponge + placebo were compared (Chapman et al. 2006). Surgeons in this study were permitted per-protocol to switch any patient from their blinded randomization group to the active treatment (sponge + thrombin) if bleeding seemed excessive (termed "rescue therapy"). The need for rescue therapy in this study was found to be lower in the thrombin-treated group than in the comparison placebo group: only 10% patients randomized to the thrombin group received rescue therapy (9/93 sites, 10%) while 20% of patients randomized to the placebo group received rescue therapy (18/90 sites, 20%).

*Reduced Blood Loss During Surgery*

Improved time to haemostasis has the potential for reduced blood loss during surgery. Reduced blood loss yields a positive benefit to the surgeon (improved visualization of surgical field) and the patient (the potential for an improved clinical outcome). However, blood loss is difficult to accurately measure experimentally for practical reasons.

Partial nephrectomy and hepatic surgery are examples of surgeries where a "prompt and durable haemostasis" is required (Richter et al. 2003). Good success has been reported during laparoscopic partial nephrectomy with the use of flowable haemostats with thrombin, avoiding the intracorporeal suturing of the renal parenchyma, which is both time consuming and high risk (Richter et al. 2003). In a case-series where flowable gelatin + thrombin was used for haemostasis for partial nephrectomy surgery (using both a laparoscopic and a retroperitoneal approach), no difference in blood loss was reported between the two surgical approaches and no decreases in haemoglobin or postoperative bleeding occurred (Richter et al. 2003).

Mathiasen and Cruz (2004) report that reduced bleeding during adenoidectomy surgery in children resulted in lower blood loss (2.5 ± 9.2 mL average blood lost in flowable gelatin + thrombin group vs. 29.4 ± 27.1 mL lost in cautery only group, $p<0.001$). This resulted in a positive impact on the surgeon's ability to perform surgery ($p<0.001$) and shorter postoperative recovery time as reported by the surgeons participating in this study.

***Safety***

Safety data from the literature review are summarised in the following table.

**Table: Published clinical trials regarding the safety of thrombin to surgical haemostat.**

| Study design | Safety endpoints | Safety results |
|---|---|---|
| **SPONGE + THROMBIN VS. SPONGE + PLACEBO** | | |
| Chapman et al. 2006<br><br>Gelfoam®/Surgifoam® (GEL/SURGI)+THR (recombinant human), (n=88) vs. GEL/SURGI+Placebo (n=42)<br><br>Note: patients were randomized initially to 66 placebo and 64 THR patients; per-protocol rescue therapy resulted in the proportions above.<br><br>THR dose 1000IU/mL<br><br>Surgery (liver, spine, peripheral vascular or vascular)<br>Prospective, multicenter, randomized, placebo controlled, double-blind<br>Total n=130<br><br>*Phase 2 study for US Approval of Recothrom® | AEs, antibody formation | Groups had similar surgery types and demographics. All patients received GEL/SURGI, either with or without THR. Patients were evenly randomized, but per-protocol, were permitted use of THR during procedure as needed for "rescue therapy," so use of THR was greater than placebo alone.<br>Safety: Serious AEs were similar between groups (24% THR vs. 19% placebo). Overall AE profile similar between groups and expected for surgical procedures, but occurrence of events in THR groups greater than placebo (e.g., nausea, constipation, insomnia, vomiting were higher in THR group than in placebo), unexplained difference but AEs transient and mild/moderate intensity.<br><br>+THR +PLAC<br>Nausea 45 26<br>Constipation 27 12<br>Insomnia 19 5<br>Vomiting 13 2<br><br>No evidence of effect on laboratory parameters or coagulation parameters.<br>Antibody formation: Antibody titres showed a similar proportion of patients with pre-existing antibodies in both groups, and one patient per group developed antibodies while on study. Reason for antibodies in non-exposed patient was unclear. |
| **SPONGE + THROMBIN (HUMAN) VS. SPONGE + THROMBIN (BOVINE)** | | |
| Chapman et al. 2007<br><br>GEL/SURGI+THR-H (recombinant human), (n=205) vs. GEL/SURGI+THR-B (Bovine) (n=206)<br><br>THR dose 1000 IU/mL<br><br>Surgery (liver, spine, peripheral vascular or vascular)<br><br>Prospective, multicenter, controlled,<br>double-blind<br><br>Total n=401<br><br>*Phase 3 study for US Approval of Recothrom® | AEs, clinical laboratory testing, coagulation parameters, presence of antibodies; pre-surgery and at 4-week follow-up | Groups had similar baseline characteristics of age gender, type of surgery.<br>Safety profiles similar between groups, AE profile similar between groups, including plausibly related AEs: thromboembolic, cardiac, hypersensitivity, postoperative wound infections, other infections showed no difference between groups. Deaths reported not related to treatment (2 in THR-B vs. 1 in THR-H). See Antibody formation, Post-hoc analysis below.<br>e.g. +THR(B) +THR(H)<br>Bleeding 11 13<br>Thromboembolic 5 6<br>Hypersensitivity 17 14<br>Infections 15 12<br><br>Laboratory results similar between groups, coagulation parameters similar.<br><br>Antibody formation: Post-treatment antibody formation was statistically lower in THR-H group than THR-B group, 1.5% vs. 21.5%, p<0.0001. |

| | | |
|---|---|---|
| | | Post-hoc analysis of bleeding/thromboembolic events, hypersensitivity, and abnormal aPTT in the 1-month post-op period showed numerically higher number of events in patients in the THR-B group who developed anti-THR-B antibodies than in patients who did not develop antibodies (not statistically different). |
| **FLOWABLE GELATIN + THROMBIN (BOVINE) VS. SPONGE + THROMBIN (BOVINE)** | | |
| Weaver et al. 2002<br><br>Floseal® (FLO, bovine origin, n=43) vs. Gelfoam® (GEL) + THR (Bovine) (n=46)*<br><br>Vascular surgery (e.g., carotid endarterectomy, AV fistula)<br><br>Prospective, multicenter, randomized, controlled<br><br>Total n=90<br><br>* Part of a Fusion Medical Technologies-sponsored study | Morbidity at 30 days and 6-8 weeks post surgery<br><br>Blood chemistry (pre- and post-treatment), blood hematology (pre-and post-treatment), clotting factors, antibody titres and factor Va antibodies | Groups had similar intra-operative heparin, gender distribution, and age distribution.<br><br>Safety analysis: Blood chemistry comparison, no differences between groups, no postoperative bleeding complications. Five patient deaths (GEL+THR) were not treatment related.<br><br>Antibody formation:<br>Serum bovine antibody titres increased from baseline in 6/38 patients (15.8%) in FLO and 3/38 patients (7.9%) GEL+THR group, difference NS (p=0.48). Serum bovine factor Va titres increased from baseline in 10/38 (26.3%) and 8/38 (21%) patients (p=0.788). These changes were not correlated with an effect on coagulation parameters. |
| Renkens et al. 2001<br><br>Proceed (PRO, n=65) vs. GelFoam® (GEL)+THR (Bovine) (n=62)*<br><br>Spinal surgery (e.g., discectomy with fusion, decompression surgery)<br><br>Prospective, multicenter, randomized, controlled<br><br>Total n=127<br><br>*Part of a Fusion Medical Technologies-sponsored study | 8 weeks post surgery<br><br>Blood chemistry (pre- and post-treatment), Blood hematology (pre-and post-treatment), clotting factors, antibody titres | GEL+THR group. There were procedure-related differences such as procedure time and blood loss; however these differences were the same in both treatment groups.<br><br>Safety: The one patient death (GEL+THR) was not treatment-related. Three AEs at the incision site in the PRO group and one similar event in the GEL+THR group were considered "possibly related" to the hemostatic agent, but all AEs successfully resolved. Blood chemistry and hematology samples revealed some differences from control that were considered not clinically significant.<br><br>Antibody formation: Antibody titres (to thrombin and to factor Va) were not statistically significantly different between the groups. Antibodies to bovine thrombin developed in 10/65 PRO patients and 10/62 GEL patients. Factor Va developed in 17/65 PRO patients and 15/62 GEL patients (p=1.0 for thrombin antibodies and 0.83 for Factor Va). These changes were not correlated with an effect on coagulation parameters. |
| Oz et al. 2000<br><br>Floseal® (FLO, n=48) vs. GelFoam® (GEL)+THR-B (Bovine) (n=45)<br><br>Cardiovascular surgery (e.g., Cardiopulmonary bypass)<br><br>Prospective, multicenter, randomized, controlled | Morbidity at 30 days and 6-8 weeks post surgery<br><br>Blood chemistry (pre- and post treatment), blood hematology (pre-and post- | Groups had similar distribution of severity of bleeding. Analysis of hemostasis in patients before and after protamine reversal of heparinisation in patients was statistically significantly better with FLO compared to GEL+THR (p=0.0023).<br><br>Safety: Blood chemistry comparison, no clinically significant differences between groups. Five patient deaths in each group were not treatment related. |

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| Total n= 93<br><br>*Part of a Fusion Medical Technologies-sponsored study | treatment), clotting factors, antibody titres | Two AEs at the incision site in the FLO group and two similar events in the GEL+THR group were considered "possibly related" to the hemostatic agent, but all AEs successfully resolved.<br><br>Antibody formation:<br>Serum bovine antibody titres were as follows:<br>Pre-trt Post-trt<br>FLO 1/48 pos THR Ab 9/48 pos THR Ab<br>GEL 0/45 pos THR Ab 12/45 pos THR Ab<br>FLO 3/48 pos fact. Va Ab 11/48 pos factor Va Ab<br>GEL 1/45 pos fact. Va Ab 15/45 pos factor Va Ab<br><br>Group differences NS (p=0.757 and 0.428, respectively). There was no evidence of increased coagulopathy at the post-recovery time point. |
| **FLOWABLE GELATIN THROMBIN (BOVINE)** | | |
| Woodworth et al. 2009<br><br>SURGIFLO™ haemostatic matrix (porcine gelatin) with Thrombin-JMI®<br><br>Endoscopic sinus surgery<br><br>Multi-centre, prospective, single-arm<br><br>Total n=30 | Adverse events, postoperative healing (30 days after surgery) | |
| **FLOWABLE GELATIN + THROMBIN (BOVINE) VS. CAUTERY OR OTHER HAEMOSTATS** | | |
| Mathiasen and Cruz 2004<br><br>Floseal® (FLO) (Bovine gelatin/THR), n=35) vs. cautery (n=35)<br><br>ENT surgery in Children (adenoidectomy)<br><br>Prospective, multicenter, randomized, controlled single-blind<br><br>Total n=70 | Complications, pain level, narcotic use return to regular diet, return to school | Groups had similar demographics and diagnosis.<br><br>Safety: No complications were reported in either group.<br><br>Three subjects in the cautery group were placed in the FLO group due to excessive bleeding, but no FLO patients had cautery (per protocol). |
| Nasso et al. 2008<br><br>Floseal® (FLO + THR (B), n=209) vs. alternate agents (ie. Surgicel Nu-Knit or Gelfoam, n=206)<br><br>Cardiac surgery<br>Prospective, randomized | Complications, postoperative morbidity, length of stay | Safety: The postoperative morbidity rates (11 FLO and 12 alternate agents), incidences of minor complications, and incidences of major complications were not statistically different ($p$ = 0.97, 0.32, 0.95, respectively). |
| **CASE SERIES USING FLOWABLE GELATIN + THROMBIN** | | |
| Fiss et al. 2007<br><br>FLO (Floseal®)<br><br>Retrospective analysis<br>n=7 out of 478 patients | Adverse events, neurological exam | Patients were retrospectively identified from 478 consecutive patients who had acute intense or persistent bleeding during intracranial surgery patients. Two patients had coagulation disorders. Two patients required additional measures to achieve haemostasis. All patients successfully treated.<br><br>Safety: No adverse events from treatment. |
| Richter et al. 2003 | Safety: | 16 M, 9 F, age 42 to 71 (mean 53), tumor size |

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| FLO (Floseal®)<br><br>Partial nephrectomy for renal cell carcinoma<br><br>Case series, single center<br><br>N=25 consecutive patients | Rebleeding at site | median 2.8 cm; laparoscopic partial nephrectomy (n=10) or retroperitoneal approach (n=25).<br><br>Safety: No cases of rebleeding were observed.<br><br>Intraoperative blood loss was reported for the two surgical approaches and was not statistically different (118±33 mL for retroperitoneal, 109±53 mL for laparoscopic approach).<br><br>No blood transfusions required, no decrease in hemoglobin values. |
| Gall et al. 2002<br><br>Case series, single center<br><br>N=18 consecutive post-endoscopic sinus surgery patients | Postoperative | FLO was removed after hemostasis in 12/30 operative sites using saline irrigation, with no adverse consequences.<br><br>Follow-up examination revealed normal healing of operative sites. |

**Additional safety data from studies with fibrin sealants**

Ten clinical studies conducted with EVICEL®/CROSSEAL® (US name for QUIXIL®) to date in the following indications: joint replacement (4), liver surgery (3), vascular surgery (2), retroperitoneal and intra-abdominal surgery in urologic, gynecologic and colorectal procedures (1). A total of 368 patients were treated with 1 to 20 mL of EVICEL®/CROSSEAL®; reported adverse events were consistent with the patients' medical conditions and the surgical procedures performed.

Six serious adverse events were considered possibly or probably related to treatment. Five of these events occurred during studies in vascular surgery; 3 were infections, 1 was a hematoma and bleeding at the operative site and 1 was a graft occlusion. One serious adverse event, an abdominal abscess which occurred in a patient in the EVICEL® group during the study in retroperitoneal and intra-abdominal surgery, was assessed by the investigator as unrelated but by the sponsor as possibly related to study treatment.

Clinical laboratory results showed no indication of effects of EVICEL®/CROSSEAL® on systemic coagulation parameters after surgery.

There were no seroconversions observed among patients who had been treated with EVICEL®/CROSSEAL® during joint replacement. One seroconversion during liver surgery was thought to be attributable to allogeneic blood transfusion and two seroconversions in patients who had received liver transplants were explained by infection via the graft and by a delayed response to vaccination. Viral serology was not monitored during the trials in vascular surgery.

**Additional safety data from the post-marketing setting**

The latest post-marketing safety reports of EVICEL® and CROSSEAL® (QUIXIL®) provide additional safety data for the use of human thrombin as ancillary substance in haemostasis medical devices. CROSSEAL® was first licensed in Israel (as QUIXIL®), in August 1997 and has subsequently been licensed in more than 20 countries including 13 countries in the European Economic Area and the USA (approved in March 2003). Currently, QUIXIL® is marketed in the UK, France, Belgium, Italy, and Mexico and has been replaced by EVICEL® in most other countries.

To date, there have been three spontaneous reports of serious adverse events that were considered possibly or probably related to CROSSEAL®. All three cases involved the use of CROSSEAL® in spinal surgery and the events were thought to be related to the presence of tranexamic acid (TA) in CROSSEAL®. The potential neurotoxicity of TA required that contact of CROSSEAL® with the CSF,

dura mater, brain, or spinal cord should be avoided. However, the re-formulation of the product without TA (as EVICEL®) means that this safety concern no longer exists. Other data from animal studies showed no indication of safety problems.

Moreover, a Product Safety Summary Report of the 11 previous quarterly Periodic Safety Update Report (PSUR) for Evithrom [Thrombin, Topical (Human)] was submitted.

Two reports of ADR have been received: one (non-serious) of lack of efficacy and one (serious) of post-operative hypotension, bradycardia and eventual cardiac arrest. There was insufficient information to determine causality.

## 2.4.2. Clinical safety of the medical device

No clinical studies with SURGIFLO™ Haemostatic Matrix Kit were submitted. A post-marketing surveillance report for SURGIFLO™ Haemostatic Matrix kit since its USA approval on 2 October 2009 was submitted. Only one adverse event (hypotension and mild arrest) was reported and no causality association was made between the adverse event and the product.

## 2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device

Controlling bleeding during surgery is critical to both the patient and the surgeon. Bleeding must be controlled to avoid serious patient morbidity and to improve patient recovery by reduction of blood loss, and enhance the surgical process by increasing visualization of the surgical field. The addition of thrombin is expected to enhance the haemostatic effect of the gelatin device (Flowable Gelatin Matrix) by combining an active mechanism (aids in fibrin clot formation) to the passive mechanism of the device (aids in platelet plug formation). As a result, more than 90% of haemostasis is achieved within 6 minutes. Although not formally demonstrated in clinical trials this added benefit was shown in animal studies (see non-clinical section).

The application of human thrombin and of human thrombin incorporated into Gelatin Flowable Matrix devices has a safe record of use. The labelling of the product contains appropriate precautions, warnings and contraindications relevant for the combined product.

The suitability of the human thrombin to achieve its intended action and any potential inherent risks due to this are justified in relation to the benefit to be obtained within the intended purpose of the device. Overall, the clinical benefit/risk profile of human thrombin and its incorporation into SURGIFLO™ Haemostatic Matrix Kit is considered favourable.

## 2.4.4. Discussion and conclusion on the clinical evaluation

No clinical studies were conducted with SURGIFLO™ Haemostatic Matrix Kit. One clinical study report was provided in support of the safety and efficacy of topically applied thrombin using SURGIFOAM®, an absorbable gelatin sponge manufactured of the same porcine gelatin. However, there are differences not only between the applied matrix devices (gelatin sponge versus Flowable Gelatin (pliable) Matrix) but also between the thrombin preparations used (liquid frozen versus lyophilised). Therefore, the equivalence of different thrombin preparations (lyophilised or liquid frozen) has been transferred from non-clinical-studies (comparability study: porcine bleeding spleen model).

The usefulness of thrombin incorporated into gelatin matrix was further evaluated through literature review. Overall, the provided literature review summarises the evidence from published human clinical studies regarding various preparations adding thrombin to a Flowable Gelatin Matrix haemostatic

product, as proposed by the applicant in the SURGIFLO™ Haemostatic Matrix Kit. These published studies generally support the clinical efficacy and safety of gelatin matrix with thrombin.

Clinical trial and post-marketing data of the approved fibrin sealants, EVICEL® and QUIXIL® (liquid frozen thrombin combined with a fibrinogen component) are also applicable regarding the safety of thrombin in combination with other components. In such combinations and depending on the type of surgery, common adverse reactions are thrombosis/occlusion of vascular grafts and focal infection. The probability of allergic reactions is low with human thrombin but there is a risk of thromboembolic event and Disseminated Intravascular Coagulation (DIC), and a higher risk of anaphylactic reaction, if the product is inadvertently injected intravascularly. Finally, no report of seroconversion for transfusion-related viruses was proven to be associated with these products during over 10 years of use.

In addition, post marketing data reported for the thrombin itself as a medicinal product (EVITHROM®) and for SURGIFLO™ Haemostatic Matrix (device without thrombin) and SURGIFLO™ Haemostatic Matrix Kit (device including thrombin) marketed in the US do not raise concerns for the safe use of these products.

The risks of the gelatin device are well known.

- The excessive amount of product that is not needed to maintain haemostasis should be removed in order to minimise tissue reaction. Overpacking in confined sites should be avoided since the gelatin swells approximately 20% upon contact with additional fluid and can migrate. This is especially important when used in proximity to foramina in bone, areas of bony confines or the spinal cord where there is a potential for nerve damage.
- Gelatin-based devices may serve as a nidus for infection and abscess formation.
- Foreign body reactions, encapsulation or accumulation of sterile fluid, and haematoma have been observed at implant sites.

It is contraindicated in:

- closure of skin due to mechanical interference with the healing of skin edges;
- intravascular compartments due to risk of embolization
- known allergies to porcine gelatin.

There does not appear to be any foreseeable reason why the incorporation of human thrombin would specifically enhance or change the risks of the device apart from adding the intrinsic risks of human thrombin, i.e.:

- thrombosis, DIC, and anaphylaxis when injected intravascularly
- allergic reactions
- vascular graft thrombosis
- antibody development but with uncertain clinical consequences
- theoretical risk of transfusion-related infection.

In conclusion, the safety of the ancillary substance thrombin is well-known as topical solution, component of fibrin sealants and in combination with haemostatic (e.g. gelatin) matrices. By extrapolation of these clinical data, there is no direct evidence about the occurrence or higher frequency of adverse events using SURGIFLO™ Haemostatic Matrix kit.

Overall, it can be deduced that the safety profile of the new SURGIFLO™ Haemostatic Matrix Kit incorporating human thrombin is similar to the safety profile of other haemostatic matrix products combined with human thrombin.

## *2.5. Overall conclusions*

**Overall conclusions on the quality and safety including the clinical benefit/risk profile of the ancillary medicinal substance in the context of its use in the medical device**

Studies have been performed to optimize and validate critical steps in the manufacturing process to guarantee consistent quality and safety of the ancillary substance human thrombin. Concerning quality the present consultation application is considered acceptable.

Since the pharmacological and toxicological profile of thrombin is well understood and no new information will be expected by further animal studies performed with SURGIFLO™ Haemostatic Matrix Kit, the non-clinical concept for thrombin is considered appropriate, in general.

Based on the provided clinical data and referenced information it is concluded that the rationale for using human thrombin in relation to the specific intended purpose of the device is sufficiently evaluated and substantiated by the applicant. According to the overall provided safety information it can be deduced that the safety profile of the SURGIFLO™ Haemostatic Matrix Kit incorporating human thrombin is similar to the safety profile of other haemostatic matrix products combined with human thrombin. The clinical benefit/risk profile of human thrombin and its incorporation into SURGIFLO™ Haemostatic Matrix Kit is considered favourable.

## *2.6. Recommendation*

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality and safety including the benefit risk profile of human thrombin used as ancillary medicinal substance in medical device, SURGIFLO™ Haemostatic Matrix Kit, was favourable and therefore granted a positive opinion in the consultation procedure.