European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CORE SPC FOR PLASMA DERIVED FIBRIN SEALANT/HAEMOSTATIC PRODUCTS (CPMP/BPWG/153/00)

DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	September 1999 November 1999 May 2000 November 2000 February 2001
DISCUSSION IN THE PHARMACOVIGILANCE WORKING PARTY	April 2001
DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	June 2001 November 2001
TRANSMISSION TO THE CPMP	December 2001
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TRANSMISSION TO CHMP	July 2004
FINAL ADOPTION BY THE CHMP	July 2004
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*** Note:**

Additional consultation period due to changes made to Section 4.1 after the previous consultation period. This consultation is specifically on section 4.1 and the related section 5.1.

CORE SPC
FOR
PLASMA DERIVED FIBRIN SEALANT/HAEMOSTATIC PRODUCTS *

The QRD Product Information template with explanatory notes and the convention to be followed for QRD templates** provide general guidance on format and text and should be read in conjunction with the core SPC and the Guideline on Summary of Product Characteristics.*
*In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products. (CPMP/BPWG/BWP/561/03).****

* The scope of this core SPC is industrially manufactured fibrin sealant/haemostatic products. It does not cover the contribution of other components, such as a collagen sponge, or medicinal products such as antibiotics.

* http://www.emea.eu.int/htms/human/qrd/qrdplt/H01a%20EN%20NOTE%20SPC-II-lab-pl%20v6.pdf
** http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconventionv6.pdf
*** http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name of the product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1:

Human Fibrinogen

[Other active substances: Product specific: factor XIII (if more than 10 U/ml), anti-fibrinolytics (e.g. aprotinin, tranexamic acid).]

Component 2:

Human thrombin

[Other active substances: Product specific.]

Quantitative composition:

[Product specific. If the concentration is expressed as weight per volume, the active substance quantity should be given for one ml of reconstituted solution.]

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

<Sealant>< Powder and solvent for sealant><solution for sealant><{other}>.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment where standard surgical techniques are insufficient (see 5.1):

- for improvement of haemostasis

[Product specific depending on whether specific clinical studies have been undertaken:]

<(to include application through a flexible endoscope to stop bleeding)>

<- as a tissue glue to promote adhesion/sealing, or as suture support:

<In vascular surgery.>

<In gastrointestinal anastomoses.>

<For tissue adhesion/sealing and suture support in neurosurgery and surgical procedures where contact with cerebro-spinal fluid or *dura mater* can occur e.g. otologic, rhinologic, ophthalmic and vertebral surgery.>

<{In other indications, specify}>>

4.2 Posology and method of administration

The use of {(Invented) name of the product} is restricted to experienced <physicians><surgeons>.

Posology

[Product specific:]

The <volume> <amount> of {(Invented) name of the product} to be applied and the frequency of application should always be oriented towards the underlying clinical needs for the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualised by the treating physician. In clinical trials, the individual dosages have typically ranged from {x} to {y} ml *[product specific]*. For some procedures {(e.g. liver traumata, or the sealing of large burned surfaces)}, larger volumes may be required.

The initial <volume> <amount> of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

[Further detailed dosage recommendations: product specific]

Method and route of administration

For epilesional use.

Prepare the solutions as described at 6.6. *[Product specific]*

Before application, the surface of the wound should be as dry as possible. See 6.6 for more detailed instructions.

4.3 Contraindications

{(Invented) name of product} must not be applied intravascularly.

Hypersensitivity to the active substances or to any of the excipients.

<*[Product specific for products containing tranexamic acid:]*

Products containing tranexamic acid should not be used in neurosurgery or surgical procedures where contact with cerebro-spinal fluid or *dura mater* can occur (e.g. otologic, rhinologic, ophthalmic and vertebral surgery) due to the risk of cerebral neurological toxicity (such as oedema and seizure).>

4.4 Special warnings and special precautions for use

For epilesional use only. Do not apply intravascularly.

<Adequate data are not available to support the use of this product in <tissue glueing> <neurosurgery> <application through a flexible endoscope for treatment of bleeding> <in vascular surgery> <or> <in gastrointestinal anastomoses.>

Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

Before administration of {(invented) name of product} care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

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

[Product specific:]

<*{(Invented) name of product}* contains bovine protein (aprotinin). Even in case of strict local application, there is a risk of anaphylactic reaction, linked to the presence of bovine aprotinin. The risk seems higher in case of previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records.>

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

[Product specific:]

<Administration of *{(invented) name of product}* in the endoscopic treatment of gastrointestinal bleedings can cause tissue damage, which can lead to formation of intramural haematoma. Abdominal pain, nausea, or vomiting within 1 to 3 days after such endoscopic treatment can constitute symptoms of intramural haematoma. In patients with intramural haematoma of the duodenal wall, pancreatitis has been reported in single literature cases. Therefore, differential diagnosis for pancreatitis should be carefully evaluated.>

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to <*[product specific]* aprotinin (see 4.4) or other> constituents of the product.

<Administration in the endoscopic treatment of gastrointestinal bleeding can cause tissue damage, which can lead to formation of intramural haematoma (see 4.4.).>

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

Inadvertent intravascular injection could lead to thromboembolic event and DIC, and there is also a risk of anaphylactic reaction (see 4.4).

[The text to be inserted here for transmissible agents, should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]

[Data on the frequency of undesirable effects for the specific product should be included here in line with the general provision of the SPC guideline (e.g. as a table according to MedDRA terminology).]

4.9 Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics, ATC code: B02BC

<Tissue adhesives, ATC code V03A K>

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both, the conversion of fibrinogen and the crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated. <Proteolytic degradation of fibrin is inhibited by anti-fibrinolytics *[product specific indicate anti-fibrinolytic used]*.>

[Product specific. Provide information on supportive trials including, where relevant, endoscopic treatment, neurosurgery, vascular surgery, gastrointestinal anastomoses, and experience in children. For example:]

<Clinical studies demonstrating haemostasis and suture support were conducted in {x} patients in {specify type} surgery.>

5.2 Pharmacokinetic properties

{(Invented) name of the product} is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

<*[Product specific]* Pharmacokinetic studies in different species of laboratory animals were conducted.> Fibrin Sealants/haemostatics are metabolised in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

This medicinal product must not be mixed with medicinal products other than appropriate solvents mentioned in 6.6.

6.3 Shelf life

[Product specific]

6.4 Special precautions for storage

[Product specific]

6.5 Nature and contents of container

[Product specific]

6.6 Instructions for use and handling and disposal

[Product specific: {instructions for reconstitution}]

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

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. <Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.>

7. MARKETING AUTHORISATION HOLDER

[Product specific]

8. MARKETING AUTHORISATION NUMBER(S)

[Product specific]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Product specific]

10. DATE OF REVISION OF TEXT

[Product specific]