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Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for plasma-derived fibrin sealant/ haemostatic products

Draft

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This guideline replaces guideline on core SPC for plasma derived fibrin sealant / haemostatic products (CPMP/BPWG/153/00).

Comments should be provided using this template. The completed comments form should be sent to BPWP Secretariat BPWPSecretariat@ema.europa.eu

Keywords	*Fibrin sealant, haemostatics, human fibrinogen, factor XIII, anti-fibrinolytics, aprotinin, tranexamic acid, human thrombin, sealant, otologic, rhinologic, ophthalmic and vertebral surgery, cerebro-spinal fluid, dura mater, glueing, neurosurgery, treatment of bleeding, vascular surgery, gastrointestinal anastomoses*

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Executive summary

This guideline describes the information to be included in the Summary of Product Characteristics (SmPC) for plasma-derived fibrin sealant / haemostatic products.

1. Introduction (background)

The purpose of this core SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of product characteristics (SmPC) for plasma-derived fibrin sealant / haemostatic products.

The QRD product information template with explanatory notes ('QRD annotated template')[1] and the convention to be followed for QRD templates[2] provide general guidance on format and text and should be read in conjunction with the core SmPC and the Guideline on summary of product characteristics[3]. It is very useful to provide information for health professionals on posology and method of administration at the end of the package leaflet since the SmPC is not always readily available. See the QRD annotated template for further guidance on how to present such information.

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 SmPCs and package leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 rev. 1)[4].

Timeline history of core SmPC: The original core SmPC (CPMP/BPWP/153/00) came into operation in January 2005. A revision was published for consultation in September 2011 but was put on hold awaiting the outcome of referral procedures for products used with pressurised gas fibrin sprayers. This revision concerns new statements for products recommended for use with pressurised gas fibrin sprayers.

2. Scope

The scope of this core SmPC 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.

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/12/WC500029823.pdf
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005091.pdf
[3] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119001.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.]

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

<Excipient(s) with known effect:>

<For the full list of excipients, see section 6.1.>

3. PHARMACEUTICAL FORM

[Product specific]

<Sealant>< Powder and solvent for sealant><solution(s) for sealant><other>.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment where standard surgical techniques are insufficient (see section 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> who have been trained in the use of {(Invented) name of the product}.

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]

[Paediatric population]

Method of administration

For epilesional use.
The product should only be <reconstituted><prepared>< and> administered according to the instructions <and with the devices> recommended for this product (see section 6.6).

Prior to applying {(Invented) name of the product} the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

[For products recommended for use with pressurised gas fibrin sprayers include the following text:]
<To avoid the risk of potentially life-threatening air embolism {(Invented) name of the product} should be sprayed using pressurised CO_2 gas only.
For spray application, see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure <and length of applicator tip>>.

4.3 Contraindications

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

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

[Product specific contraindications]

[For products recommended for use with pressurised gas fibrin sprayers include the following text:]
<Spray application of {(Invented) name of the product} should not be used in endoscopic procedures. For laparoscopy, see section 4.4.>

[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 precautions for use

For epilesional use only. Do not apply intravascularly.
Life-threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

[For products recommended for use with pressurised gas fibrin sprayers include the following text:]
<Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

{(Invented) name of product} spray application should only be used if it is possible to accurately judge the spray distance, especially during laparoscopy. Spray distance from tissue and pressure should be within the ranges recommended by the marketing authorisation holder of this product (see table in section 6.6 for pressure and distance).

When spraying {(Invented) name of product}, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.>

<When using accessory tips with this product, the instructions for use of the tips should be followed.>

<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.>

{(Invented) name of product} should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

<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.>

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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 rev. 1).]

<u><Paediatric population></u>

4.5 Interaction with other medicinal products and other forms of interaction

No 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 Fertility, pregnancy and lactation

The safety of fibrin sealant/haemostatic products for use in human pregnancy or during 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 post-natal 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 sealant/haemostatic products. 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 disseminated intravascular coagulation (DIC), and there is also a risk of anaphylactic reaction (see section 4.4).

<Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.>

[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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 rev. 1).]

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

<Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.>

Frequency of Adverse Reactions (ADRs) in clinical studies with {(Invented) name of product}
[Product specific: table]

Description of selected adverse reactions
[Product specific]

<Paediatric population>
[Product specific]

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 V03AK>

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.>

Paediatric population

[Product specific: The text should be in line with the Paediatric Regulation and the SmPC guideline. In case of a full waiver or any deferral, include the standard statement in the SmPC guideline.]

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 sealant/haemostatic products 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

<In the absence of compatibility studies t><T>his medicinal product must not be mixed with other medicinal products except those mentioned in section <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 Special precautions for disposal <and other handling>

The instructions for use are also described in the healthcare professionals' package leaflet part.

[Product specific: {instructions for reconstitution}]

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

[For products recommended for use with pressurized gas fibrin sprayers include the following text:]

<**Spray application**

To avoid the risk of life-threatening air embolism {(Invented) name of the product} should only be sprayed using pressurised CO_2 (see table below).

[Product specific:{handling}]

The pressure regulator should be used in accordance with the manufacturer's instructions.

When applying {(Invented) name of the product} using a spray device, it has to be ensured that the pressure and the distance from the tissue are within the ranges recommended by the marketing authorisation holder of this product, as given in the following table:

Surgery	**Spray set to be used**	**<Applicator tips to be used>**	**Pressure regulator to be used**	**Recommended distance from target tissue**	**Recommended spray pressure**

The product should then be sprayed onto the surface of the tissue in short bursts (0.1-0.2 ml) to form a thin, even layer. <{(Invented) name of the product} forms a clear film over the area of application.>

When spraying {(Invented) name of product}, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.>

<When using accessory tips with this product, the instructions for use of the tips should be followed.>

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

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 THE TEXT

[Product specific]

<Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.>