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(CHMP)**

**GUIDELINE ON THE CLINICAL INVESTIGATION OF PLASMA DERIVED
FIBRIN SEALANT/HAEMOSTATIC PRODUCTS
(CPMP/BPWG/1089/00)**

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1. INTRODUCTION

The term “fibrin sealant/haemostatic^a” denotes a product containing coagulation factors, to be administered locally in order to produce a fibrin clot. Typical fibrin sealants consist of at least two components, which are kept separately until allowed to mix. One of the components contains human fibrinogen, as substrate of the clot. Additionally, following the current Ph. Eur. Monograph, it may contain as further active substances human factor XIII to stabilise the generated fibrin clot and/or inhibitors of fibrinolysis. The other component contains thrombin, which will convert the fibrinogen in the first component to fibrin.

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

Intended benefit of the fibrin sealant application is to support local haemostasis, to “glue” surfaces of injured tissues in order to obtain adaptation or sealing of surfaces, to support sutures, or to improve repair and healing.

This Guideline describes the information to be documented to demonstrate efficacy and safety when an application for a marketing authorisation for fibrin sealant products is made. Such an application should contain data on clinical safety and efficacy. These data are necessary for:

1. products for which an application for a marketing authorisation is to be submitted, referred to as ‘new products’ in the text and
2. authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal step or purification procedures), referred to as ‘modified products’ in the text.

The clinical trials described in this Guideline should be performed according to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

1.1 Clinical use

In the human body, a fast-reacting and efficient blood coagulation system is in place, which is activated in any case of injury disrupting the integrity of blood vessels. After primary haemostasis by the adherence and aggregation of thrombocytes at the site of the injury, this physiological system produces fibrin in order to stop blood loss and to generate a matrix which supports healing. In case of injuries which are accessible, the exertion of mechanical pressure would contribute to limitation of blood loss and improvement of haemostasis.

Taking the above considerations into account, fibrin sealant kits would be needed only where a patient’s own physiological coagulation system is impaired, or does not possess the capacity to produce fibrin quickly enough in the required quantity and stability. Fibrin sealant products have been used to support haemostasis in patients with coagulopathies undergoing surgery. The mainstay of fibrin sealant use, however, is in patients without pre-existing coagulation disturbance, who require major surgery or experience major trauma, or require endoscopic procedures to stop bleeding. Fibrin sealant products are particularly in use, when

- application of mechanical pressure is not possible,
- suturing is difficult or tight tissue sealing/adhesion is required (for example in the case of extensive wound surfaces, or parenchymal organs such as the liver or lung), or
- reliable haemostasis is critical (for example in neurosurgery, where even a small haematoma may be dangerous).
- where the patient’s own physiological coagulation system is impaired.

However, fibrin sealant must not be considered a substitute for surgical hemostatic measures or

^a For readability purposes the term “fibrin sealant” is used throughout the text of this guideline.

meticulous surgical technique.

1.2 Efficacy

While in clinical evaluation of human plasma derived factor concentrates for substitution in patients with congenital deficiency, the initial trial may be one that examines the pharmacokinetics, such an approach is obviously not applicable in the case of fibrin sealant products.

Therefore, the efficacy has to be assessed in studies with objective clinical endpoints.

Fibrin sealants include a heterogeneous group of products used in different indications (e.g. improvement of haemostasis, tissue glue to promote adhesion/sealing, or as suture support). It will be necessary to design clinical studies in which the appropriate endpoint is assessed for each therapeutic indication proposed.

It is beyond the scope of this guideline to itemise all possible endpoints.

Studies should be of controlled design in order to demonstrate that the application of fibrin sealant provides measurable benefit in comparison to the spontaneous haemostasis and/or healing process under standard treatment without fibrin sealant.

Particularly it is of interest to study whether the application of fibrin sealant is of benefit to patients with anti-coagulation/anti-platelet treatment when relevant to the indications studied.

1.3 Safety

Safety aspects of fibrin sealant products include viral safety, safety with regard to TSE, immunogenicity and other adverse events.

1.3.1 Viral safety

Manufacturers of plasma products such as fibrin sealant are obliged to optimise viral safety by selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation/removal of viruses in manufacturing processes.

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.

These procedures may be of limited value against non-enveloped viruses, such as hepatitis A and parvovirus B19. The safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

The applicant is nevertheless required to provide all available data gathered on patients treated with the product in clinical trials. Investigators should continue with their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports on infection with a full investigation.

For products with a totally novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

1.3.2 Safety with regard to TSE

The safety of products with regard to the potential transmission of TSE can at the present state of knowledge not be assessed by clinical studies. Therefore, it is essential that all ruminant (bovine) material is sourced and processed as outlined in the current edition of the “Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” (EMEA/410/01).

1.3.3 Immunogenicity

Antibodies against components of fibrin sealant products may occur very rarely. In patients, where preparations containing bovine thrombin had been used, inhibitory antibodies occurred against bovine

thrombin and contaminating bovine factor V with cross-reactivity also to human factor V*, causing severe bleeding. Rarely antibodies occur after use of fibrin sealant products containing only human proteins.

Anaphylactic/allergic reactions have occurred to aprotinin, especially after re-exposure. In such patients antibodies to aprotinin were found.

1.3.4 Adverse events

All adverse events after application of the new fibrin sealant product should be recorded and reported. Since the accurate local placement of fibrin sealant is critical for the outcome, it should be evaluated whether adverse events are attributable to the product, or to the technique of application.

2. CLINICAL TRIALS WITH PRODUCTS FOR WHICH AN APPLICATION FOR A MARKETING AUTHORISATION IS TO BE SUBMITTED: 'NEW PRODUCTS'

2.1 Efficacy

Though the principle of action is uniform, fibrin sealant activity may be used in various diseases and clinical situations, as pointed out above. Since the fibrin sealant products differ significantly in their composition, application sets, and the technique of use, there is no basis for granting a marketing authorisation on the grounds of general experience with such products.

For each new product efficacy has to be demonstrated in well-designed, prospective, controlled clinical trials with measurable endpoints (see "Note for Guidance on General Considerations for Clinical Trials", CPMP/ICH/291/95 (ICH E8)). As far as possible, the comparison should be made between a control group receiving the standard treatment without fibrin sealant, and a group receiving fibrin sealant in addition to the standard treatment. Details of study design and number of patients required depend on the indication claimed. In every case, the data should be robust enough to establish the efficacy of the product in terms of improving haemostasis. The patients should be followed for a sufficient time period to assess the final outcome in terms of wound healing.

In choosing the patient population for clinical trials, particular care should be taken to ensure that the clinical situations under study represent those encountered in actual clinical practice.

If adhesion/sealing of tissues and/or suture support is also to be an indication, further specific data is required. Certain clinical applications are especially critical and demanding and will require separate clinical trials. Examples of such situations include, but are not restricted to the following:

- vascular anastomoses, since due to intravascular blood pressure, leakage might cause major blood loss, particularly in case of arterial vessels,
- gastrointestinal anastomoses, since they need to be particularly stable and durable in order to withstand intraluminal pressure and peristaltic movement and because leakage of bowel content may cause peritonitis, and
- neurosurgery, which requires particularly reliable haemostasis, since any haematoma might be dangerous due to compression of vital cerebral structures.

If neurosurgical applications are requested, a separate efficacy and safety study providing data on surgical procedures where contact with cerebrospinal fluid or dura mater can occur (e.g. otologic, rhinologic, ophthalmic and vertebral surgery) should be performed. Fibrin sealants used in neurosurgery should not contain tranexamic acid, since cerebral oedema and seizures have occurred.

If the applicant intends to apply, in addition to the regular local use, for different techniques of application, e.g. through a flexible endoscope, a clinical study to demonstrate efficacy of this approach would be required.

* Baenninger H, Hardegger T, Tobler A, Barth A, Schuepbach P, Reinhart W, Laemmle B, Furlan M. Fibrin glue in surgery: frequent development of inhibitors of bovine thrombin and human factor V. *British Journal of Haematology*, 1993;85 (3):528-32.

2.2 Safety

Clinical safety will be assessed in all patients participating in the trials for blood pressure, heart rate, temperature, respiratory rate and adverse events during treatment, and for adverse events during the follow-up period.

All adverse events should be recorded and reported in accordance with the ICH guideline “Structure and content of clinical study reports” (CPMP/ICH/137/95E3).

Viral safety

Compliance with CHMP recommendations with regard to viral safety under 1.3.1 is necessary for all plasma derived products and is verified by information supplied in Part II of the dossier.

A pre-treatment serum sample from each patient included in the clinical trials should be stored at -70°C for possible future testing.

Immunogenicity

Attention should be given to the possibility of antibodies against thrombin and other constituents. Such antibodies would cause alterations of global coagulation tests. Therefore, appropriate clotting tests should be part of the study protocol, and in case of pathological findings, specific testing for neutralising antibodies should be carried out.

Other adverse events

- As part of the clinical patient monitoring, thrombotic events should be described and the possible relationship to application of the fibrin sealant should be discussed.
- All anaphylactic reactions should be described and the possible relationship to aprotinin exposure investigated.
- Fibrin sealants containing tranexamic acid should not be used in neurosurgery. (See 2.1)

2.3 Treatment of children

Information on the clinical use of fibrin sealants in children is very limited. Therefore, any use in children should be documented and relevant information provided.

3. CLINICAL TRIALS IN CASE OF A CHANGE IN THE MANUFACTURING PROCESS OF AUTHORISED PRODUCTS: ‘MODIFIED PRODUCTS’

Introduction

The currently available fibrin sealant preparations differ with respect to composition and method of viral inactivation/removal. Changes in the manufacturing procedures may lead to significant changes in the product, including alteration of biochemical properties of the fibrin sealant components, and may thereby alter the characteristics and activity of the product. The effects of changes in the manufacturing process (e.g. viral inactivation steps or purification procedures) on the biological characteristics and activity of the product should be investigated. If significant impact on the characteristics and activity of the fibrin sealant cannot be excluded, data on efficacy and safety should also be provided with the application.

3.1 Efficacy

Evidence should be provided to demonstrate that the change in the manufacturing process has not affected the efficacy of the product. This would require at least one well-designed, prospective, comparative trial with adequately assessable measurable endpoints and with enough patients in each arm. Details of study design and number of patients required depend on the clinical particulars of the indications studied. The patients should be followed for a sufficient time period to assess the final outcome in terms of wound healing.

Such a clinical trial should focus on endpoints demonstrating either support of haemostasis, or reliable

action as tissue glue.

3.2 Safety

Please refer to requirements for new fibrin sealant products. (See 2.2)