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# Questions and answers on the review of the fibrin sealants Tisseel, Tissucol, Artiss and Beriplast P (and associated names) given by spray application

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

On 13 December 2012, the European Medicines Agency completed a review of the safety and effectiveness of the fibrin sealants Tisseel, Tissucol, Artiss and Beriplast P (and associated names), following concerns over the risk of gas embolism when these medicines are given by spray application. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines continue to outweigh their risks, but that appropriate measures have to be put in place to optimise the safe use of these medicines when they are applied as a spray during surgery.

## What are fibrin sealants?

Fibrin sealants are medicines that are used as a sealant (glue) during surgery to help reduce local bleeding. They are composed of two solutions, one containing fibrinogen and another containing thrombin, both of which are proteins involved in the blood clotting process. When the two solutions are mixed together, thrombin breaks fibrinogen up into smaller units called fibrin. The fibrin then aggregates (sticks together) and forms a fibrin clot that helps the wound to heal, stopping the bleeding.

Several fibrin sealants have been authorised in European Union (EU) Member States through national procedures. These include Quixil, Tisseel, Tissucol, Artiss and Beriplast P (and associated names). Evicel is the only centrally authorised fibrin sealant for use by spray application.

Fibrin sealants can be applied by dripping or spraying the solution onto bleeding tissue. For Evicel, Quixil, Tisseel, Tissucol and Artiss, the solution is currently sprayed using either pressurised air or carbon dioxide ($CO_2$). Beriplast P does not require a gas-assisted spray device.

## Why were fibrin sealants reviewed?

Following cases of gas embolism (presence of a gas bubble in the blood that affects the blood flow) reported in association with the use of Evicel and Quixil, in May 2012 the European Commission asked the CHMP to issue an opinion on whether the marketing authorisation for Evicel should be maintained,

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varied, suspended or withdrawn across the EU. At the same time, the United Kingdom medicines agency requested a similar assessment for Quixil and for the other fibrin sealants authorised in EU countries, given that the risk of air embolism could not be excluded for these products. Due to the close similarity of Evicel and Quixil, the CHMP concluded its review of Evicel and Quixil in November 2012[1]. The current conclusions concern Tisseel, Tissucol, Artiss and Beriplast P (and associated names).

## Which data has the CHMP reviewed?

The CHMP reviewed the available safety data on fibrin sealants from clinical studies, post-marketing use and the published literature, focusing on reported cases of confirmed or suspected gas embolism. The Committee also considered the spray devices used together with these medicines, and the benefit of giving fibrin sealants by spray application. A group of experts in blood products, haemostasis (the stopping of bleeding) and surgery was also consulted.

## What are the conclusions of the CHMP?

The CHMP noted that all of the cases of gas embolism seen with Evicel and Quixil were related to the use of the spray device at higher-than-recommended pressures or in closer proximity to the tissue surface than recommended.

As Beriplast P (and associated names) does not require a gas-assisted spray device, the CHMP concluded that there is no risk of gas embolism with this product when used in accordance with the prescribing advice and with the recommended device.

Regarding Tisseel, Tissucol and Artiss (and associated names), the CHMP concluded that, although the risk of gas embolism was considered very low, risk minimisation measures should be implemented when these medicines are given by spray application to help ensure they are used safely. These include the following:

- the wording of the product information should be strengthened and educational materials updated to provide clear and consistent information to surgeons on the recommended pressure and distance during spray application;
- the company for Tisseel, Tissucol and Artiss should ensure that these products are used with pressure regulators that do not exceed the maximum pressure required to deliver the fibrin sealant, and which have labels stating the recommended pressure and distance;
- the product information should include a warning that the risk of gas embolism appears to be higher when fibrin sealants are sprayed using air, as compared to $CO_2$, and patients should be closely monitored for signs of possible gas embolism.

The full changes made to the information to doctors and patients are detailed here.

The Committee also agreed that the company marketing Tisseel, Tissucol and Artiss should provide a letter to relevant healthcare professionals in the EU including important information on the safe use of these medicines.

[1] For information on the outcome of this review, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Fibrinogen-containing_solutions_for_sealant_authorised_for_administration_by_spray_application/human_referral_000329.jsp&mid=WC0b01ac05805c516f

## What are the recommendations for surgeons?

- Surgeons should note the potential risk of gas embolism with incorrect spray application of Tisseel, Tissucol and Artiss and take the necessary precautions detailed in the updated prescribing advice for these medicines. In particular, when spraying these products:
  - the recommended pressures should not be exceeded, and the sealant should not be sprayed at a closer distance than recommended;
  - patients should be closely monitored for signs of possible gas embolism (by measuring blood pressure, pulse rate, and oxygen and $CO_2$ levels in the blood).
- There is no risk of gas embolism with Beriplast P when used in accordance with the prescribing advice and with the recommended device.

The European Commission issued a decision on 15 March 2013.