20 February 2013
EMA/734308/2012 rev.1
EMEA/H/C/000898/A20/18
EMEA/H/A-31/1337

Questions and answers on the review of the fibrin sealants Evicel and Quixil given by spray application

Outcome of procedures under Article 20 of Regulation (EC) No 726/2004 and Article 31 of Directive 2001/83/EC

On 15 November 2012, the European Medicines Agency completed a review of the safety and effectiveness of the fibrin sealants Evicel and Quixil given by spray application, following cases of gas embolisms reported with these medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines given by spray application continue to outweigh their risks, but that appropriate measures have to be put in place to minimise the risk of gas embolism.

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 the other containing thrombin, which are both 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.

Fibrin sealants can be applied by dripping or spraying the solution onto bleeding tissue. The solution is currently sprayed using either pressurised air or carbon dioxide (CO_2).

Evicel is the only centrally authorised fibrin sealant. It was authorised in October 2008 and is available in 11 EU member states[1]. Other fibrin sealants in the EU are authorised nationally and these include Quixil, Tisseel, Tissucol, Artiss and Beriplast P (and associated names).

Why were fibrin sealants reviewed?

In August 2010, measures were taken to minimise the risk of gas embolism (presence of a gas bubble in the blood that affects the blood flow) following five reported cases involving Evicel or Quixil applied

[1] Austria, Denmark, Estonia, France, Finland, Germany, Ireland, Netherlands, Spain, Sweden and United Kingdom, as well as Norway.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

by spray. These included changes to the product information to specify the maximum spray pressure to use during application and the recommended distance from the tissue surface. However, since then, three further cases of gas embolism have been reported with Evicel, which were due to insufficient distance between the applicator and tissue or too high spray pressure. This indicates that the risk minimisation measures have not been sufficient.

Consequently, in May 2012, the European Commission asked the CHMP to issue an opinion on whether further measures are necessary to ensure the safe use of Evicel and on whether its marketing authorisation should be maintained, varied, suspended or withdrawn across the EU. At the same time, the UK's medicines regulatory agency requested the CHMP to carry out the same assessment for Quixil and the other fibrin sealants available in the EU.

Which data has the CHMP reviewed?

The CHMP reviewed 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 fibrin sealants have the potential to be life-saving in certain circumstances, and that applying these medicines by spray is considered to be of benefit when there is a large surface area of bleeding during certain surgical procedures. The CHMP also noted that, although cases of gas embolism are rare, there is a need to take further measures to prevent this life-threatening risk.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Evicel and Quixil continue to outweigh their risks, but that further risk minimisation measures should be implemented when these medicines are given by spray application to ensure that they are used correctly. The Committee recommended that:

- Evicel and Quixil should be sprayed using CO_2 only, instead of pressurised air, because the greater solubility of CO_2 in blood reduces the risk of embolism;
- the wording for 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;
- these medicines should not be sprayed in endoscopic surgery (a type of less invasive surgical procedure). In addition, care should be taken during laparoscopy (another type of less invasive surgical procedure) to ensure that the minimum safe distance from the tissues is observed;
- the company for Evicel and Quixil should ensure that these products are used with pressure regulators that do not exceed the maximum pressure required to deliver the fibrin sealant, and that contain labels stating the recommended pressure and distance.

The full changes made to the product information for Evicel are detailed here, and for Quixil here.

The Committee also agreed that the company marketing these medicines should provide a letter to relevant healthcare professionals in the EU explaining these risk minimisation measures.

The CHMP is still reviewing four other fibrin sealants: Tisseel, Tissucol, Artiss and Beriplast P (and associated names).

What are the recommendations for surgeons?

- Surgeons should note the potential risk of gas embolism with improper spray application of Evicel and Quixil and take the necessary precautions detailed in the updated prescribing advice for these medicines.
- Evicel and Quixil should be sprayed using CO_2 only.
- Spraying Evicel or Quixil in endoscopic surgery is contraindicated.
- Evicel or Quixil application by spray should only be considered if it is possible to accurately judge the spraying distance.

The European Commission issued a decision for Evicel on 13 February 2013 and for Quixil on 20 February 2013.