20 February 2013
EMA/66729/2013

Assessment report for Fibrinogen-containing solutions for sealant authorised for administration by spray application

Product name: Quixil

Procedure number: EMEA/H/A-31/1337

Referral under Article 31 of Directive 2001/83/EC

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 24 May 2012, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations fibrinogen-containing solutions for sealant authorised for administration by spray application should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

From 2008 until May 2012, four cases of life-threatening air embolism were reported for spray application of Quixil (of which one had a fatal outcome but without any product being administered). In the same period, 4 cases (of which two had a fatal outcome) were reported following spray application of Evicel, a second generation fibrin sealant, approved via the centralised procedure in 2008. The thrombin component of Evicel is identical to the thrombin component of Quixil but the fibrinogen component of Evicel differs mainly from that of Quixil in the fact that it does not contain tranexamic acid.

Despite risk mitigation activities put in place between August 2010 and early 2011 for Quixil and Evicel, including: 1) a direct healthcare professional communication regarding a change in product labelling, 2) field safety notification for the pressure regulator including change in the instructions for use, and 3) updated customer training programs, two new cases of air embolism (and a third one during the referral procedure) have been reported following use of the spray application of Evicel (one non-fatal case in August 2011 and a fatal case in January 2012).

Based on the above, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 on 21 May 2012, requesting the CHMP to assess the above concerns and their impact on the benefit-risk for Evicel, to give its opinion on measures necessary to ensure the safe and effective use of Evicel and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn. Following this, the UK's Medicines and Healthcare products Regulatory Agency triggered a procedure under Article 31 on 24 May 2012, requesting the CHMP to carry out the same assessment for the other fibrin sealants available in the EU, including Quixil.

Fibrin sealants (also known as tissue adhesives or glues) are used in a wide range of surgical procedures to rapidly arrest bleeding and assist in subsequent wound healing. Fibrin sealants can be applied either by drip or spray method, the choice of method being left to the surgeon depending on the degree and the surface area of bleeding expected or encountered and the remoteness of the location of the bleeding surface. When applied by spraying, in order to achieve a sufficiently fine and uniform spray, the syringe containing the fibrin and thrombin components is usually connected to a supply of gas (CO2 or compressed air) through a pressure regulator.

Although there are instructions in the current product information regarding the pressure that must be used and the distance from the bleeding tissue that must be maintained during the spray application, in order to avoid forcing gas into the vasculature, there is a concern that these instructions are not always being adhered to, leading to a risk of air embolism.
The following four products authorised in Europe for spray application were identified and considered in the context of this Article 31 procedure: Tisseel/Tissucol, Artiss, Beriplast P Combi-set and Quixil (and associated names). The active ingredients for these products vary, with the main difference being the antifibrinolytic component. Beriplast P, Tisseel/Tissucol and Artiss contain aprotinin, whereas Quixil contains tranexamic acid. Tisseel and Tissucol differ in terms of Factor XIII content.

The authorised indications for all four products are the "*supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis"* and "*to promote adhesion/sealing or as suture support*". In addition, Artiss is also indicated for "*use as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery*".

This report only includes the assessment of Quixil. Quixil is a first generation fibrin sealant containing two components, human clottable protein and human thrombin and was approved via the mutual recognition procedure in 14 European countries with the UK as reference member state. A second generation fibrin sealant, approved via the centralised procedure in 2008, is marketed under the name Evicel.

The thrombin component of Evicel is identical to the thrombin component of Quixil but the fibrinogen component of Evicel differs mainly from that of Quixil in the fact that it does not contain tranexamic acid. Evicel is indicated as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and as suture support for haemostasis in vascular surgery. Evicel and Quixil can be either dripped onto the tissue or sprayed onto the tissue in short bursts. If spraying is required, a pressure regulator has to be used with pressurized CO2 or compressed air.

Tisseel/Tissucol, Artiss and Beriplast P Combi-set have been assessed separately.

2.1. Clinical aspects

2.1.1. Clinical efficacy

A total of 8 clinical trials have been conducted using Quixil. The majority of studies involved the spray application. The intended benefit of fibrin sealant is the ability to effectively achieve haemostasis when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. This was addressed in clinical trials with Quixil in terms of time to haemostasis and blood loss (Table 1).

Table 1: Clinical Studies Summary

Study No.	Type of Surgery	Safety Analysis Set	Study Design	Main Effectiveness Parameter	Fibrin Sealant Application	Effectiveness Results
Q-LIV-008-US	Liver	Total: 121 QUIXIL 58 - Control 63	Single blind, randomized, active-controlled (range of other haemostatic products)	Time to hemostasis	Spray	91.4% vs. 69.8% 5.3 min. vs. 7.7 min.
OFI-LIV-003-B	Liver	Total: 34 QUIXIL 17 - FS Control 17	Open label active-controlled (Tissucol Kit R)	Blood loss	Spray	No difference (p=0.79)
OFI-LIV-002-UK	Liver	Total: 21 QUIXIL 21 Control 0	Open, non-controlled	Blood loss	Spray	Mean: 1300ml (SD 739mL)
Q-THR-009-US	Orthopedic (THR)	Total: 97 QUIXIL 54 Control 43	Single blind, randomized, controlled (standard care)	Mean Blood loss (total)	Spray	698.7 mL vs. 836.6 mL (p=0.007)
OFI-TKR-001-IL	Orthopedic (TKR)	Total: 59 QUIXIL 29 Control 30	Single blind, randomized, controlled (standard care)	Mean Blood loss (total)	Spray	473 mL vs. 1147 mL (p<.001)
OFI-TKR-004-US	Orthopedic (TKR)	Total: 53 QUIXIL 25 Control 28	Single-blind randomized controlled (standard care)	Mean blood loss (post-op)	Spray	185.9 mL vs. 452.3 mL (p<.001)
OFI-THR-005-UK	Orthopedic (THR)	Total: 13 QUIXIL 13 Control 0	Open pilot study, vs. historical controls	Mean blood loss reduction (total) of 3 treatment regimen	Spray	51% vs. 48% vs. 25 %
Q-CVS-015-UK	Vascular	Total: 20 QUIXIL 10 Control (Kaltostat) 10	AEs to 30 days after surgery, Hematology, Coagulation	Single blind, randomized controlled	---	---

Surgical: oxidised, regenerated cellulose haemostat, Kaltostat: calcium/ sodium alginate dressing, standard care: ligation/ cautery

Four of those 8 studies were randomized (no double-blind study design). One study compared Quixil with another fibrin sealant. No significant differences with regard to haemostasis were obtained. All 8 trials have already been assessed by CHMP as part of the marketing authorisation application for the centrally authorised product Evicel.

In order to justify the use of spray application rather than dripping, the MAH performed a literature review which showed that the spray application is considered a valuable adjunct to achieve haemostasis with the benefits of reduced blood loss and reduced need for blood transfusion in joint replacement (Levy et al, 1999), in cardiothoracic surgery (Kjaegard, 1996), and in liver surgery (Schwartz et al, 2004). Furthermore, a Cochrane review (Carless et al, 2009) found that, in contrast to the drip application, the spray application provides a more uniform film and is therefore more appropriate for diffuse bleeding or bleeding from large tissue surfaces. The spray technique is considered to facilitate the application of fibrin sealant to remote surgical sites (Spotnitz, 2001), and can improve blood conservation and reduce intra-operative bleeding (Jackson, 2001).

The MAH also argued that there are surgical situations, e.g. large bleeding surface or remote location of bleeding, where the spray is considered to be the best option. The MAH provided three experts statements supporting this view.

With regard to the efficacy of sprayable fibrin sealants, the CHMP assessed the available information, including data submitted by the MAH. The CHMP also noted that there appears to be evidence for the need to use the combination spray sealants in situations where there is significant blood loss from a wide surface area and the survival of the patient is threatened. The CHMP therefore concluded that the available evidence supports the efficacy and utility of Quixil in the approved indications.

2.1.2. Clinical safety

A comprehensive search for any case or safety issue that might reveal or be symptomatic of gas embolism was conducted by the MAH, including product quality complaints or device incident reports.

The search confirmed the 4 cases of gas embolism previously reported for Quixil. In one of them which had a fatal outcome, the equipment was significantly modified by the surgeon and the patient did not receive treatment with Quixil fibrin sealant or its applicator. The 3 other cases associated with Quixil are described below.
The 4 cases of air embolism associated with Evicel, of which 2 were fatal, are described in the CHMP AR on the Article 20 review of Evicel, which was assessed in parallel to this procedure.

A first case of air embolism was reported in association with the Tissomat pressure regulator, which was used to spray Quixil during a hepatectomy procedure. The Quixil spray was used 10 to 15 cm from the target organ (pressure used was not specified). The patient did not experience any difficulties or complications during the pressurised Quixil application. During surgery, the patient was in a supine position and experienced a decrease of ACT oxygen, vascular collapse along with the presence of air in the hepatic vein and inferior vena cava. Due to the pulverisation, the patient developed an air embolism, which led to a small hemodynamic collapse and severe desaturation that resolved within minutes. The symptoms occurred immediately after the Quixil application, without any change in the patient's position. The patient is reported to have recovered.

A second case of air embolism involved a patient who developed an air embolism following the use of Quixil during an unspecified vascular surgery procedure. In this case, a gush of air released from the delivery device was suspected to have travelled up the patient's artery causing a life-threatening air embolism. Appropriate clinical action was taken, and the patient recovered.
A third life-threatening air embolism case was reported following the use of Quixil sprayed at less than 5cm distance from the tissue surface (recommended distance 10-15cm) and at a higher pressure range from 2 to 3 bars (recommended pressure range 2.0-2.5 bars) on the liver resection site. A few seconds later the patient's heart rate decreased from 80 to 25 beats per minute and systolic arterial pressure decreased from 110 to 30 mmHg. Simultaneously central venous pressure increased from 2 to 28 mmHg and end tidal CO_2 decreased from 4.65 to 2.26 kPa. Repeated injections of epinephrine (total 15 mg) and norepinephrine (total 30 mg) and cardiopulmonary resuscitation were necessary for the next 25 minutes, followed by continuous infusion of both drugs (both at 4 mg/hour). Trans-oesophageal echocardiography (TOE) showed bubbles in both ventricles, deriving from the inferior vena cava. A low-density floating thrombus (3cm in size) was observed in the right ventricle. The air

embolism was confirmed by trans-oesophageal echocardiography (TOE). The patient is reported to have recovered without sequelae.

In each case there was a failure to follow at least one of the current instructions on administration of spray application of Quixil using pressurised gas:

1. Inappropriate distance from the tissue surface
2. Excessive pressure
3. Use on open vessels or within a highly vascular cavity e.g. bone marrow.

In addition, a search for any serious and fatal adverse reactions was performed, which identified 28 cases with a fatal outcome for Quixil or Evicel. The majority of the adverse reactions were either related to underlying disease or reasonably explained by surgical and/or post-operative complications.

The MAH stated that the spray device does not represent a risk of gas embolism as long as the instructions for use are complied with, and that the observed cases gas embolism associated with Quixil applied by spray are linked to misuse or unfamiliarity with the proper method of administration.

The CHMP reviewed all cases of gas embolism reported with the use of sprayable fibrin sealants. The analysis of the case reports showed that symptomatic air/gas embolism had occurred only when the instructions for use were not followed; in most cases, the spray application was made at pressures higher than the recommended pressure and/or at distances to the target tissue surface lower than the recommended distance.

The CHMP therefore concluded that a number of serious incidents with severe patient harm or death have occurred in association with sprayable fibrin sealants and that the potential link to the gas system cannot be ignored. The CHMP also agreed that there is no risk of gas embolism associated with the fibrin sealant itself or when the sealant is applied by the drip method.

Overall, the concern is regarding the long-term effectiveness of the current educational material and/or training program to reduce the risk of air embolism and whether re-training with an assessment component to test individuals' learning would be more appropriate. In the third quarter of 2010, a Dear Doctor Letter and a field safety notification were issued, warning of the risk of gas embolism when the spray was applied at pressures higher than recommended and/or at distances shorter than recommended to the site of bleeding. This was followed up with an updated SmPC with the same warning in the first quarter of 2011. Between August 2010 and the start of this referral procedure, two additional case reports with the spray application of Evicel have been reported (a case of air embolism with a fatal cardiac arrest and a case of life-threatening cardiac arrest, severe abrupt hypotension, bradycardia and abrupt loss of end-tidal carbon dioxide). These reports demonstrate that the actual risk minimization measures are not effective to sufficiently reduce the risk of air embolism.

During the Article 31 procedure, the CHMP also noted a new case of gas embolism reported with the use of Evicel during laser prostatectomy. Evicel was sprayed antero-laterally via pressure regulator with N2 (nitrogen) for a single two-second burst at approximately 2½ to 3 centimetres with reduced pressure of 8 (eight) PSI. This case occurred during a clinical trial and highlights the problems with the application of sprayable fibrin sealants during endoscopic procedures, where it is not always feasible to judge distances (such as 4cm) accurately when spraying. As a result, gas embolism may occur even with a reduced pressure.

The CHMP noted that the difference in composition between Quixil and Evicel results in a higher viscosity for Quixil, which in turn has the consequence that more force is required to deliver spray application of Quixil. The pressure range for Quixil is therefore higher (2.0-2.5 bar) compared with that of Evicel (1.0-1.7 bar). The CHMP noted that despite the different recommended pressure regulator settings the fibrin sealant spray systems may have similar gas velocity. Moreover, the CHMP concluded that there was insufficient evidence to substantiate a higher risk of air embolus for Quixil (relative to Evicel) because of the different pressure range required for Quixil.

In conclusion, with regard to safety, the CHMP noted that the main risk with sprayable fibrin sealants is the risk of air/gas embolism, due to air/gas entering the vasculature. The CHMP therefore considered that correct administration of sprayable fibrin sealants is essential to reduce this risk and focused its assessment on this risk and the identification of measures that would be necessary and adequate to minimise this risk.

An ad-hoc expert advisory group meeting was convened in October 2012 at the request of the CHMP, during which the experts discussed the benefits of sprayable fibrin sealants as well as potential risk minimisation measures, in particular with regard to the risk of air embolism. The experts agreed that sprayable fibrin sealants are recommended when there is a large surface area of surgical bleeding, generally oozing, and that not using sprayable fibrin sealants in these cases would lead to an increased use of other blood products, which would lead to a higher risk of complications. The expert unanimously agreed that the risk of air embolism is not related to the medicinal product itself but to the device design and its misuse in practice. They were of the opinion that CO2 should be used instead of air as a safety precaution because of the markedly lower risk of gas embolism due to the high solubility of CO2 in the blood. Furthermore, the device design should have a specific gas pressure governor to be used with the spray applicator and with a limit not above the maximal optimal pressure recommended. They also recommended that appropriate educations materials and training for healthcare professionals to administer the product correctly (at the recommended distance and pressure for spray application) is required.

The MAH was also asked to discuss the merits and feasibility of any risk minimisation measures which could be introduced in order to improve the benefit/risk of the Quixil spray application.

2.2. Risk minimisation activities

No risk management plan (RMP) was submitted by the MAH.

The CHMP identified and agreed upon a number of risk minimisation measures to be implemented by the MAH to reduce the safety concern of air/gas embolism associated with sprayable fibrin sealants.

The MAH shall ensure that, at the time of the European Commission decision for this procedure (EMEA/H/A-31/1337), all users of the spray application of this product are provided with educational material. This material shall inform about the

- risk of life-threatening gas embolism if the product is sprayed incorrectly
- use of pressurized CO_2 only
- restriction to open surgery
- correct pressure and distance from tissue
- requirement to dry the wound using standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices) prior to using the product
- requirement to closely monitor blood pressure, pulse rate, oxygen saturation and end tidal CO_2 when spraying the product, for the occurrence of gas embolism.
- which regulator(s) should be used, in line with manufacturer recommendations and the SmPC instructions for use

The material shall include the latest Summary of Product Characteristics and the section titled “The following information is intended for medical or healthcare professionals only” of the latest package leaflet.

The MAH shall offer an educational program to all users of the spray application of this product. The program shall teach the content of the mentioned educational material.

The Marketing Authorisation Holder shall agree the exact content and format of the educational material and educational program with the national competent authority.

The MAH shall ensure that, within three months of the European Commission decision on this procedure (EMEA/H/A-31/1337), all users of the spray application of this product are provided with

- labels for the pressure regulator that inform about the correct pressure and distance in open surgery
- a warning card that informs about the correct pressure and distance for the spray application for open surgery
- a yellow tag, to be placed on the device air hose, which provides instructions for use. If the tag is provided as part of the medicinal product, it should be incorporated in the product information via a variation procedure

The MAH shall ensure that, within two years of the European Commission decision on this procedure (EMEA/H/A-31/1337), the product can only be used with a pressure regulator that caps the maximum pressure at 2.5 bars.

The Marketing Authorisation Holder (MAH) shall submit to the national competent authorities, within one month of the European Commission decision on this procedure (EMEA/H/A-31/1337), an EU risk management plan for the product according to the EU Good Vigilance Practices which includes the safety concern of gas embolism and the above-listed risk minimisation measures.

2.3. Changes to the Product Information

The CHMP revised the Quixil product information in accordance with the agreed risk minimisation measures, to ensure the safe and effective use of Quixil. The major changes to the SmPC was the amendment of Section 4.2, to reflect the fact that the use of Quixil is restricted to experienced surgeons who have been trained in the use of Quixil and the Method and Route of Administration section was extensively revised, to reflect the risk of air embolism (also in Section 4.4 and 4.8) and to state that Quixil should only be used with a pressure regulator device that delivers a maximum pressure of no more than 2.5 bar and uses carbon dioxide gas only. Clarity on the appropriate means of achieving a tissue surface that is as dry as possible were also added, together with a sentence reminding users to comply with the recommendations on the required pressure and distance from tissue (also in Section 4.4). In Section 4.3, a contra-indication in use in endoscopic procedures was added. Section 4.4 was additionally revised to remind users that Quixil spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer. Section 6.6 was amended to add a table clarifying the pressure and distance from tissue recommended by the manufacturer and include the recommendation that Quixil should only be sprayed using carbon dioxide gas.

In the Package Leaflet, a sentence was added to Section 2 stating that Quixil should not be used in endoscopic surgery or for keyhole surgery and text was also added to inform users of the risk of embolism and reminding them to use only carbon dioxide gas and to comply with the recommendations for pressure ranges and spraying distance from the tissue surface. In Section 3, a sentence restricting the use of Quixil to experienced surgeons who have been trained in the use of Quixil was added, together with a table clarifying the pressure and distance from tissue recommended by the manufacturer.

For detailed changes please refer to the Annex III of the CHMP opinion.

3. Overall discussion and benefit/risk assessment

Having considered the available data, the MAH's responses and taking into account with the ad-hoc advisory group recommendations, the CHMP identified and agreed upon a number of risk minimisation measures to be implemented by the MAH to reduce the risk of air/gas embolism associated with sprayable fibrin sealants. In particular, the MAH was requested to submit an EU risk management plan to the national competent authority which includes the safety concern of gas embolism and to ensure that all users of the spray application are provided with adequate educational material on the correct use of the product and are offered an educational program which teaches the content of the mentioned educational material. In addition, the MAH should ensure that all users of the spray application of this product are provided with labels for the pressure regulator that inform about the correct pressure and distance in open surgery, a warning card that informs about the correct pressure and distance for the spray application for open surgery and a yellow tag, to be placed on the device air hose, which provides instructions for use. Finally, the product should only be sprayed using pressurised carbon dioxide gas and the MAH should ensure that the product can only be used with a pressure regulator that caps the maximum pressure at 1.7 bars.

Regarding the clinical use of the product, the CHMP was of the opinion, based on the last case of air embolism that was reported during an endoscopy procedure, where the surgeon has limited visibility of the tissue surface that the use of Quixil by spray application should only be considered if it is possible to accurately judge the spraying distance. Spraying Quixil in endoscopic procedures should therefore be contra-indicated. Clear instructions to surgeons with regard to the distances and pressures recommended and the pressurised gas to be used should be provided and the use should be restricted to experienced surgeons who have been trained in the use of Quixil.
Appropriate means of achieving a tissue surface that is as dry as possible should be used and changes in blood pressure, pulse, oxygen saturation and end tidal CO2 should be monitored during application of Quixil by spray because of the possibility of occurrence of air or gas embolism. The CHMP revised the Quixil PI accordingly, to ensure the safe and effective use of Quixil (see Annex III).

Benefit / risk balance

Having considered all the available data, including the MAH responses provided in writing and during oral explanations and the conclusions of the ad-hoc expert meeting, the CHMP agreed that the benefit-risk balance of Quixil as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis, remains positive under normal conditions of use, subject to the changes to the product information, (see Annex I and IIIB), together with the agreed risk minimisation measures (see Annex II) and the agreed Direct Healthcare Professionals Communication.

4. Action plan

4.1. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate the outcome of the present review. The MAH confirmed that the shipment of Quixil in Europe had ceased in May 2012 and that only very few units of Quixil were available in France and Italy. The CHMP agreed that the DHPC should be circulated to all Quixil users (Operating Room Directors, Theatre managers, Materials Managers, Theatre Nurses, Hospital Pharmacists and Risk Managers) in France and Italy, no later than 30 November 2012.

The final version of this DHPC agreed by the CHMP was provided together with the communication plan.

5. Overall conclusion

Having considered all the available data, including the MAH responses provided in writing and during oral explanations and the conclusions of the ad-hoc expert meeting, the CHMP agreed that the benefit-risk balance of Quixil as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis, remains positive under normal conditions of use, subject to the changes to the product information, (see Annex I and IIIB), together with the agreed risk minimisation measures (see Annex II) and the agreed Direct Healthcare Professionals Communication.

Divergent positions are appended to this Assessment Report.

6. Conclusion and grounds for the recommendation

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC fibrinogen-containing solutions for sealant authorised for administration by spray application, including Quixil;
- The Committee reviewed all the data provided by the MAH in writing and in the oral explanation and the outcome of the ad-hoc expert advisory group meeting;
- The Committee considered all the cases of air embolism associated with the use of Quixil by spray application that have been reported and concluded that the risk minimisation measures previously implemented were insufficient to mitigate the identified risk of air embolism associated with the use of the Quixil spray application;
- The CHMP agreed on a number of additional risk minimisation measures, including changes to the product information regarding the use of the product as well as educational materials and training to be provided to users of the product, which adequately addressed the identified risk of air embolism;
- The Committee, as a consequence, concluded that the benefit-risk balance of Quixil as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis, is positive under normal conditions of use, subject to the agreed risk minimisation measures, including changes to the product information.

Therefore the CHMP recommended the variation to the terms of the Marketing Authorisations for the medicinal products referred to in Annex I, in accordance to the amendments to the Summary of

Product Characteristics and Package Leaflet set out in Annex III and subject to the conditions set out in Annex IV.

7. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.

8. Appendix

Divergent positions dated 15 November 2012

Divergent positions

Procedure No: EMEA/H/A-31/1337
Quixil and associated names

The undersigned CHMP members expressed their divergent views with regards to the Opinion given by the CHMP within the Article 31 procedure for fibrinogen containing solutions for sealants authorised for use by spray application. The reasons for the divergent views are summarized as follows:

- Quixil is effective in its licensed indications and has been used in drip and spray application for various surgical procedures. However, there is no evidence of particular advantages of Quixil versus alternative authorised fibrin sealant products.
- Evidence of harm in relation to spraying is based on 4 spontaneous cases of air embolism following spray application of Quixil at higher than recommended pressure and/or in close proximity to the tissue surface. Of these 4 cases, one fatal case was unusual as the pressure regulator was modified to attach a needle to it during an arthroscopy procedure but no product was applied. Although limited usage data is available for spray application of Quixil, it appears that the reporting rate for Quixil may be higher than other fibrin sealant products.
- The lack of further cases of air embolism in association with Quixil spray application since 2010 does not demonstrate safety of the product and may be explained by the diminishing usage of Quixil.
- The differences for the reporting rates are not well understood however, it is possible that the higher viscosity of Quixil and the consequential higher pressure required to spray it may be contributing factors, despite some evidence of similar gas velocities between products in experimental settings.
- In light of the evidence suggesting a potentially higher risk, and the physical differences between Quixil and other sprayable fibrin sealants, and as some of the possible risk factors (e.g. higher viscosity and required pressure) are not amenable to risk minimisation, the benefit-risk balance of the spray application is considered negative.

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Dr. Robert Hemmings	15 November 2012	Signature:
Dr. Conception Prieto Yerro	15 November 2012	Signature:
Dr. Jacqueline Genoux-Hames	15 November 2012	Signature:
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