

15 March 2013 EMA/96130/2013

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

Product name: Tisseel and associated names Tissucol and associated names Artiss and associated names Beriplast and associated names

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, 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 for fibrinogencontaining solutions for sealant authorised for administration by spray application should be maintained, varied, suspended or withdrawn.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, a total of eight cases of life-threatening air embolism were associated with the spray application of the fibrin sealant Quixil or Evicel (of which three had a fatal outcome, in one case no product was administered).

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use of Evicel and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.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, i.e. Quixil, Tissucol, Tisseel, Artiss, Beriplast P, 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 Tisseel/Tissucol and Beriplast P are the "supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis" and "to promote adhesion/sealing or as suture support". Artiss is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples. In addition, ARTISS is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces.

Fibrin sealants can be applied either by drip or spray method, the choice of method is left to the surgeon depending on the degree and surface area of bleeding expected or encountered and the remoteness of the location of the bleeding surface. When applied by spraying and 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 through a pressure regulator.

Although there are instructions in the current product labelling for use regarding the pressure that must be set and the distance from the bleeding tissue that must be maintained during the spray application in order to avoid forcing gas into the vasculature and the risk of air embolism, there is a concern that these instructions are not always being adhered to, leading to a risk of air embolism.

The products are administered using certain accessories and pressure devices as summarised below.

Product	Surgical procedure	Accessories	Pressure device
Tisseel/Tissucol**	Open wound surgery	- Easyspray set	Easyspray/Tissomat*
	Minimally invasive/laparoscopic procedures	- Duplospray MIS Applicator	Duplospray MIS Pressure regulator
Artiss	Open wound surgery	- Easyspray set	Easyspray
Beriplast P#		 Pantajet (includes spray tip) Catheject Spray-tip – Beriject Endoflex 	Not applicable
Quixil		Double barrel syringe with standard 6 inch flexible tip which consists of three lumens: two larger lumens where fibrinogen and thrombin components are expelled and maintained separately and third lumen for introducing air/gas source to assist spray application.	Omrix pressure regulator (operated by foot pedal)

* Tissomat is no longer sold, but installed units are still in use

** Tisseel and Tissucol are different products in terms of FXIII content

Beriplast P not sprayed using automated pressure. A pressure regulator cannot be attached to the spray system

On 15 November 2012, the CHMP concluded the review of Quixil (for which four cases of lifethreatening air embolism were reported) and agreed 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 changes to the product information and implementation of risk minimisation measures, including educational materials and training to be provided to users of the product.

This report only includes the assessment of Tisseel, Tissucol, Artiss and Beriplast P (and associated names).

2.1. Clinical aspects

2.1.1. Clinical efficacy

The MAHs were asked to provide a justification and relevant supporting data/evidence for the use of their spray application taking into account all available evidence for efficacy of the spray application in the approved indications, the clinical situations for which using a sprayable fibrin sealant is more advantageous than other applications and the risks to the patient of not using a sprayable application.

Tisseel/Tissucol and Artiss

The clinical rationale for using aerosolised (spray) application for surgical sealants is provided below.

In open surgery, the tissue surfaces that are surgically manipulated are often considerable. Some typical examples are: resection of large areas of parenchymal organs (e.g. liver, lung) the exposure of large bone spongiosa areas (e.g. sternotomies) or the detachment or resection of large areas of the skin and subcutis in esthetic, reconstructive or burns procedure. All these clinical instances are often

associated with considerable bleeding (capillary oozing) which requires intra-operative haemostasis or sealing of larger surfaces to prevent re-bleeds or air leaks.

There are also surgical situations in which the application of a thin, even layer of product is critical for a good wound healing (Tisseel/Artiss) or for prevention of thick layer of product that due to swelling may compress adjacent tissues.

In all these clinical situations the use of the standard cannulas or applicators for the product delivery is ineffective, time consuming and non-economic. To be able to apply a fibrin or surgical sealant on these surfaces the use of the spray method is the only feasible option.

The same applies to minimally invasive (laparoscopic) surgery. Liquid fibrin-based (Tisseel/Artiss) or synthetic surgical sealants are often required to provide sealing of hollow organs, haemostasis and even adhesion prevention in endoscopic procedures. There are also surgical situations in which the application of a thin, even layer of product is critical for a good wound healing (Tisseel/Artiss) or for prevention of thick layer of product that due to swelling may compress adjacent tissues.

The clinical studies performed with Tisseel/Tissucol (4 studies) and Artiss (5 studies) are described in the table below:

Study number	Fibrin sealant used	Surgical procedure	Application Devices used	Total number of evaluable subjects	Number of subjects exposed to gas- assisted spray application
550904	Tisseel	Hepatic resection	Easyspray plus Spray set	70	35
550001	Tisseel	Total hip replacement	Tissomat plus Spray set and blunt cannula	100	26 (phase A) and 27 (phase B)
550002	Tisseel	Sealing Auxillary Lymph node dissection sites	Tissomat plus Spray set	161	79
550003	Tisseel	Cardiac surgery	Blunt cannula and Tissomat plus Spray set	317	87
520001	Artiss	Skin grafts in burns patients	Tissomat and Spray set	40	40
550201	Artiss	Skin grafts in burns patients	Tissomat and Spray set	138	138
550703	Artiss	Facelift	Easyspray and Spray set	45	45
550901	Artiss	Facelift	Easyspray and Spray set	75	75
550902	Artiss	Abdominal plasty	Easyspray and Spray set	40	20
All studie	ès 🗌			986	572

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Efficacy was demonstrated in the four randomised clinical studies performed with Tisseel in various surgical procedures (such as hepatic, cardiac and total hip replacement surgery). A total of 254 subjects were exposed to the spray application of Tisseel in these studies. No adverse events of air embolism were reported.

Furthermore, the clinical benefits of spray application of Tisseel/Tissucol in various minimally invasive/laparoscopic procedures (including hernia mesh fixation, partial nephrectomies, hepato-biliary surgery) have been reported in a number of peer-reviewed publications. Those publications provide evidence that spray application of Tisseel/Tissucol decreases early postoperative pain, persisting or chronic inguinal pain and therefore reduces the need for analgesia and may also reduce operative time. A publication by Lau et al. from 2005 indirectly demonstrated the downsides of not using a laparoscopic spray device in hernia mesh fixation. This is a randomised prospective trial that demonstrated a significant reduction of analgesic requirement by using Tisseel for mesh fixation during endoscopic treatment of inguinal hernia. The authors also concluded that Tisseel is safe and efficacious alternative to mechanical stapling for the anchorage of mesh during inguinal hernia surgery.

For Artiss, efficacy was demonstrated in the five clinical studies conducted in a number of subcutaneous surgical procedures (e.g. skin grafts, facelift and abdominal plasty). A total of 318 subjects were exposed to the spray application of Artiss. No adverse events of air embolism were reported.

In laparoscopic surgery, the abdomen is already insufflated with CO2 at a pressure of 10-15 mm Hg (pneumoperitoneum). This insufflation itself has been reported as the source of air embolism throughout the years. This is why CO2 has been established as a standard for abdominal laparoscopic insufflation, since CO2 has the lowest risk for air embolism. Using pressurised gas, spraying should not add to the intra-abdominal pressure and different gases should not be combined. A specific pressure regulator has been designed to connect to CO2 and deliver extremely low flow rates with minimal increase of the surface tissue pressure.

The determination of the laparoscopic spraying safety parameters for DuploSpray MIS has been performed based on (tissue) surface pressure testing over a distance of 1 mm – 100 mm at three different flow rate settings (1.0, 2.0, and 2.5 standard liter per minute (SLPM)). The MAH recommended testing at adequate benchmark testing (tissue surface pressure in a vented laparoscopic environment) with a pneumoperitoneum pressure of 12 - 15 mm Hg, and at distances of 0 - 7 cm.

Based on the in vitro testing (pressure transducer method) the following medical safety recommendation has been provided: minimal spraying distance: 2 cm; optimal spraying distance: 3 cm. This has been tested at a range of distances to 0 to 7cm with a pneumoperitoneum pressure of 12 – 15 mm Hg. This works at low pressure even at high flow rate and has a vent line allowing gas an escape route from within the peritoneum prevented pressure rise.

According to the current SmPC, Artiss is only indicated for subcutaneous use and therefore it is presumed it cannot be used for laparoscopic surgery.

The CHMP commented that an in depth report of the relevant clinical trials conducted on these products and how they can be used in the various different clinical scenarios has been provided. The explanation given for the need for gas pressurized delivery was considered well balanced.

Beriplast P

An overview of five clinical studies on the use of Beriplast in different surgical procedures was provided by the MAH which was extracted from regulatory submission documents submitted for EU Marketing authorization. The MAH states that it is demonstrated that in none of the pivotal clinical studies in which the spray method of Beriplast was applied a gas-assisted spray device was used (normally applying pressures between 1.5 to 2.0 bar of CO_2 , air or nitrogen).

The CHMP commented that no meaningful data could be extracted with regard to efficacy but there was no indication of any change in the efficacy profile of the product.

Conclusion

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 of 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 use of fibrinogen-containing sealants in the approved indications, under normal conditions of use.

2.1.2. Clinical safety

The CHMP reviewed all cases of gas embolism reported with the use of sprayable fibrin sealants (including the cases reported with Quixil and Evicel). The analysis of the case reports showed that symptomatic air/gas embolism had occurred only when the instructions for use were not followed; in each of the other cases there was a failure to follow at least one of the current guidelines on administration of spray application of fibrin sealants using pressurised gas:

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

In one of the Quixil cases, the air embolism was caused by using pressurised air to dry the wound area, with a fatal outcome, although no product was administered. The CHMP pointed out that surgeons and surgical staff should be advised on the appropriate means of achieving a tissue surface that is as dry as possible (e.g. intermittent application of compresses, swabs, use of suction devices).

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 highlights the problems with the application of sprayable fibrin sealants during endoscopic procedures, where it is not always feasible to judge distances accurately when spraying. As a result, gas embolism may occur even with a reduced pressure.

Tisseel/Tissucol and Artiss

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

The cases related to air embolism reported with those products are summarised below.

One report was identified that was also reported to the product quality department as the pressure device Easyspray was also implicated. The report was received in 2009 and describes a patient who developed an air embolus when Tisseel was inadvertently sprayed into a closure port by the surgeon. This case followed incorrect use of gas with different gas source adaptor (CO_2 instead of medical air or nitrogen) and the application to a closure port (low distance, high pressure) may have contributed to the serious air embolism.

A second non-fatal case of air embolus was reported in association with Tissomat pressure regulator that was used to spray Quixil. This case involved a sequence of three user errors: 1) use of the Tissomat with a fibrin sealant other than Tissucol, with an unknown spray set; 2) use of higher than recommended pressure (>2 bars) using a defective pressure device and 3) application of the pressurised fibrin sealant on a tear of a sub-hepatic vein (intravascular).

No cases of air embolism have been reported in association with spray application of Artiss in open wound surgery using the Easyspray pressure regulator.

Beriplast P

The search performed by the MAH revealed that no cases of air embolism have been reported in association with Beriplast P. The MAH has received two Product Technical Complaint reports relating to the device Pantaject but none reported an air embolism.

Conclusion

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 experts 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 clinical 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 educational materials and training for healthcare professionals to administer the product correctly (at the recommended distance and pressure for spray application) is required.

In conclusion, with regard to safety, the CHMP noted that the main risk with sprayable fibrin sealants is the risk of air embolism, due to air 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. However the CHMP noted that to date, only one non-fatal case of air embolism has been reported for these products as compared to the 8 cases of air embolism (including 3 cases with fatal outcome) reported with Quixil and Evicel.

2.2. Risk minimisation activities

Tisseel/Tissucol and Artiss

The MAHs provided responses to a request from the CHMP to discuss the merits and feasibility of any risk minimisation measures which could be introduced in order to improve the benefit/risk of Tisseel, Tissucol and Artiss spray application.

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

The MAH shall ensure that all users of the spray application of this product and all internal personnel are provided with educational material that shall inform about the

- risk of life-threatening gas embolism if the product is sprayed incorrectly
- correct pressure and distance from tissue depending on kind of surgery (open or laparoscopic)
- for laparoscopic surgery restriction to only use if the minimum spray distance of 2 cm (recommended range 2-5 cm) can be accurately judged and with CO2 only (only for Tisseel and Tissucol as not applicable for Artiss)
- 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 CO2 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 also ensure that all users of the spray application of this product are provided with labels for the pressure regulator with a symbol that informs about the correct pressures and distances in open and laparoscopic procedures.

The MAH should ensure within two years, that the product is used in accordance with the SmPC, with a pressure regulator device that delivers a maximum pressure of no more than 2.0 bar (28.5 psi) in open wound surgery.

The MAH should ensure within two years, that the product is used in accordance with the SmPC, with a pressure regulator device that delivers a maximum pressure of no more than 1.5 bar (22 psi) in minimally invasive/laparoscopic procedures.

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 Pharmacovigilance Practices (EU GVP) which includes the safety concern of gas embolism and the above-listed risk minimisation measures.

Beriplast P

The CHMP did not require the MAH to submit a Risk Management Plan. No additional risk minimisation measures addressing the risk of air embolism were considered necessary by the CHMP for this product.

2.3. Changes to the product information

Tisseel/Tissucol and Artiss (and associated names)

The CHMP revised Tisseel/Tissucol and Artiss product information in accordance with the agreed risk minimisation measures, to ensure the safe and effective use of those products.

The major changes to the SmPC was the amendment of Section 4.2, to reflect the fact that the use of Tisseel/Tissucol and Artiss is restricted to experienced surgeons who have been trained in the use of the products and the Method and Route of Administration section was extensively revised, to reflect the risk of air embolism (also in Section 4.4) and to state that in open wound surgery the products should only be used with a pressure regulator device that delivers a maximum pressure of no more than 2.0 bar (Tisseel/Tissucol and Artiss) and in minimally invasive/laparoscopic procedures, they should only be used with a pressure regulator device that delivers a maximum pressure of no more than 1.5 bar and uses carbon dioxide gas only (Tisseel/Tissucol). In addition, the section 4.2 of Artiss SmPC was amended to include that Artiss is not recommended in laparoscopic procedures. 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). Section 4.4 was additionally revised to remind users that Tisseel/Tissucol and Artiss spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer and to add the warning that the risk of gas embolism appears to be higher when fibrin sealants are sprayed using air, as compared to CO2 and cannot be excluded with Tisseel/Tissucol and Artiss, especially when used in open wound surgery. Only carbon dioxide gas should be used in minimally invasive/laparoscopic procedures (Tisseel/Tissucol). Finally, the recommendation to monitor changes in blood pressure, pulse, oxygen saturation and end tidal CO2 when spraying Tisseel/Tissucol and Artiss, because of the risk of air embolism, was also added. Section 6.6 was amended to add a table clarifying the pressure and distance from tissue recommended by the manufacturer.

In the Package Leaflet, a sentence was added to Section 2 to inform users of the risk of embolism that appears substantially higher when fibrin sealants are sprayed using air, as compared to CO2 and cannot be excluded with Tisseel/Tissucol and Artiss, especially when used in open wound surgery.

A reminder to use carbon dioxide gas only in minimally invasive/laparoscopic procedures (Tisseel/Tissucol) and to comply with the recommendations for pressure ranges and spraying distance from the tissue surface was also inserted in this section.

In Section 3, a sentence restricting the use of Tisseel/Tissucol and Artiss to experienced surgeons who have been trained in the use of those products 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.

Beriplast P and associated names

The CHMP revised Beriplast P product information, to ensure optimal safe use of the product. Clarity on the appropriate means of achieving a tissue surface that is as dry as possible was also added in section 4.2 (also in section 6.6) as well as a sentence reminding that the product should only be reconstituted and administered according to the instructions and with the devices as provided with this product. The Package Leaflet was amended accordingly.

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

3. Overall discussion and benefit/risk assessment

Tisseel/Tissucol and Artiss

Having considered all available data, the MAH's responses and 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 the spray use of Tisseel, Tissucol and Artiss. The CHMP noted that for these products only one non-fatal case of air embolism has been reported.

In particular, the MAH was requested 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 those products are provided with labels for the pressure regulator with a symbol that informs about the correct pressure and distance in open surgery. For Tisseel and Tissucol, which are also recommended for use in laparoscopic procedures, a label for the pressure regulatory with a symbol that informs about the correct pressure and distance laparoscopic procedures should also be provided.

Artiss is only indicated for subcutaneous use. It is not recommended for use in laparoscopic surgery.

Finally, Tisseel/Tissucol and Artiss should only be sprayed using a pressure regulator that limits the maximum pressure at 2.0 bar when used in open wound surgery and using a pressure regulator device that deliver a maximum pressure of 1.5 bar when used in minimally invasive/laparoscopic procedures.

Regarding the clinical use of the products, the CHMP was of the opinion, based on the last case of air embolism reported during an endoscopy procedure with Evicel, where the surgeon had limited visibility of the tissue surface that the use of fibrin sealants with compressed gas should only be considered if it is possible to accurately judge the spraying distance.

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 those products. 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 those products by spray because of the possibility of occurrence of air or gas embolism.

Tisseel/Tissucol use different pressure regulators for open surgery (pressurized air) and minimally invasive/laparoscopic procedures (pressurized CO2), respectively. CHMP considered restricting spray application of these products to CO_2 gas only. However, technical requirements when limiting spray application to CO_2 gas were considered to add uncertainties to the clinical use of those products, e.g.

in minimally invasive/laparoscopic surgery where the maximal pressure to be applied is 1.5 bar, the pressure regulator intended for open wound surgery that allows a higher pressure, could be used by mistake, or the handling associated with CO₂ cylinders and respective pressure reducing connectors in the operating theatre. The anticipated benefit of mandating CO₂ use in open surgery may not outweigh the risks linked to inappropriate use of Tisseel/ Tissucol and Artiss. Considering the limited evidence of risk of air embolism with those specific products (Tisseel/Tissucol and Artiss), CHMP concluded that beyond the above mentioned risk minimisation measures no further actions were deemed justified and that the use of carbon dioxide should not be mandatory for the spray application using a pressure regulator of those products. The CHMP however recommended the inclusion in the Product information of the warning that the risk of gas embolism appears to be substantially higher when fibrin sealants are sprayed using air, as compared to CO2 and cannot be excluded with Tisseel/Tissucol and Artiss, especially when used in open wound surgery. In minimally invasive/laparoscopic procedures (Tisseel/Tissucol), only carbon dioxide gas should be used.

The CHMP revised recommended changes the Product Information of Tisseel, Tissucol and Artiss accordingly, to ensure the safe and effective use of those products (see Annex III).

Beriplast P

Beriplast P is not sprayed using automated pressure regulator. It employs manual pressure derived by the syringe applicator and therefore, no gas-assisted spray device is available for Beriplast P. An attachment of air feeding lines or other device components to the manual spray tips physically is not possible. The risk of air embolism was therefore considered negligible by the CHMP.

In order to minimise the potential risk of Beriplast P being used with a pressure regulator not recommended for use with this product, the CHMP recommended that the PI of Beriplast be amended to emphasize that Beriplast should only be reconstituted and administered according to the instructions and with the devices as provided with this product. In addition, in line with the changes requested for the other fibrin sealants used by spray, the PI was amended to reflect that appropriate means of achieving a tissue surface that is as dry as possible should be used (see Annex III).

4. Action plan

4.1. Direct Healthcare Professional Communication

Tisseel/Tissucol and Artiss (and associated names)

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate the outcome of the present review. The CHMP agreed that the DHPC should be circulated to the following groups of healthcare professionals, in all EU Member States where Tisseel/Tissucol and Artiss are marketed: all surgeons, including consultant surgeons, concerned theatre managers, all theatre nurses, and all hospital pharmacists, no later than 15 January 2013.

5. Overall conclusion

Tisseel/Tissucol and Artiss

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 Tisseel, Tissucol and Artiss in their approved indications, is positive under normal conditions of use, subject to the changes to the product information, (see Annex III), together with the agreed risk minimisation measures (see Annex IV) and the agreed Direct Healthcare Professionals Communication.

<u>Beriplast P</u>

Having considered all the available data, including the MAH written responses and the conclusions of the Ad-hoc Expert meeting, the CHMP agreed that the benefit-risk balance of Beriplast P as supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis

(including endoscopic treatment of bleeding gastroduodenal ulcer) and as a tissue to promote adhesion/sealing or as suture support, is positive under normal conditions of use, subject to the changes to the product information, (see Annex III).

6. Conclusion and grounds for the recommendation

Grounds for the variation to the terms of the marketing authorisation of Tisseel/Tissucol and Artiss (and associated names)

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC fibrinogencontaining solutions for sealant authorised for administration by spray application;
- 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 fibrinogensealants by spray application that have been reported and concluded that the reported cases had only occurred when the instructions for use were not followed.
- The Committee agreed on a number of 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 the spray application of fibrinogen-sealants 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 Tisseel/Tissucol and Artiss medicinal products (and associated names) 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.

Grounds for the variation to the terms of the marketing authorisation of Beriplast P

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC fibrinogencontaining solutions for sealant authorised for administration by spray application;
- The Committee reviewed all the data provided by the MAH in writing 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 fibrinogensealants by spray application that have been reported and concluded that the reported cases had only occurred when the instructions for use were not followed;
- The Committee has considered that as no gas-assisted spray device is available for Beriplast and that an attachment of air feeding lines or other device components to the manual spray tips is not possible, the risk of air embolism with Beriplast is negligible;
- The Committee, as a consequence, concluded that the benefit-risk balance of the spray application of Beriplast P is positive under normal conditions of use, subject to 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.

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.