07 December 2012
EMA/66677/2013
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Evicel

Human Fibrinogen / Human Thrombin

**Procedure number:** EMEA/H/C/000898/A-20/0018

## 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

The scope of the review was the assessment of the potential association of Evicel with life-threatening air embolism. From 2008 until May 2012, four cases of life-threatening air embolism (of which two had a fatal outcome) were reported following spray application of Evicel.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 21 May 2012 to assess the above concerns and its impact on the benefit/risk for Evicel, and 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use of Evicel, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.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 authorised in the EU.

A further case of air embolism in association with Evicel was received during the Article 20 procedure.

# 2. Scientific discussion

Evicel is a second generation fibrin sealant containing two components, human clottable protein and human thrombin and was approved via the centralised procedure in 2008.

Evicel is indicated as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. It is also indicated as suture support for haemostasis in vascular surgery.

From 2008 until May 2012, four cases of life-threatening air embolism (of which two had a fatal outcome) were reported following spray application of Evicel. A further case of air embolism in association with Evicel was received during this review procedure. In the same period, 4 cases were associated with the spray application of Quixil, a first generation fibrin sealant, approved via the mutual recognition procedure. 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 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. The choice of method of application is 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 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.

Despite risk mitigation activities put in place between August 2010 and early 2011, 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 review procedure) have been reported following the 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.

## *2.1. Clinical aspects*

### 2.1.1. Clinical efficacy

A total of 3 clinical trials have been conducted using Evicel and 8 clinical trials using Quixil (first generation Omrix fibrin sealant). The majority of studies involved spray application. Four Quixil studies and two Evicel studies are randomized.
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 Evicel/Quixil in terms of time to haemostasis and blood loss (Tab. 1 and 2).

**Tab. 1. Evicel - Clinical Studies Summary**

| Study No. | Type of Surgery | Safety Analysis Set | Study Design | Main Effectiveness Parameter | Fibrin Sealant Application | Effectiveness Results |
|---|---|---|---|---|---|---|
| 400-05-006 | Urological Gynecological General | Total 135* EVICEL 67 - Control 68 | Randomized Controlled Trial (vs. Surigel) | Time to hemostasis (within 10 minutes) | Drip and Spray | 95.5% vs. 81.2% |
| 400-05-001 | Vascular | Total: 147 EVICEL 75 - Control 72 | Randomized Controlled Trial | Time to hemostasis | Drip | 85.3 %vs. 38.9% |
| 400-08-004 | Vascular | Total 100 EVICEL 100 - Control 0 | Single Arm Registry | NA | Drip | NA |

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

**Table 2: Quixil - 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%<br>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

For Evicel there is only 1 study available in which both drip and spray applications were used, the other two studies used only drip application. The majority of studies with Quixil have been conducted using the spray method. There is a lack of data providing a direct comparison between Evicel and Quixil applied by drip or spray methods within a study.

In general, the sample size of the studies for Evicel/Quixil in different indications is considered small and only 6 studies are randomized (no double-blind study design). One study compared Quixil with another fibrin sealant. No significant differences with regard to haemostasis were obtained. All 11 clinical trials have already been assessed by the CHMP.

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 Evicel 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 Evicel. Those cases are described below. The cases of air embolism associated with Quixil are described in the CHMP AR on the Article 31 referral on fibrinogen-containing solutions for sealant, which was assessed in parallel to this procedure.

A fatal case of air embolism was reported in a patient who underwent an initial hysteroscopy and subsequent second hysteroscopy for recurrent bleeding. Evicel was sprayed to control cervical bleeding. One minute after application there was full cardiac arrest and death. The post-mortem exam showed air within the vasculature including brain and heart. One possible explanation for the event under consideration of the reporters was that the gas in the circulatory system was as a result of the use of the spray applicator in an enclosed space.
The pressure regulator was set at 37 psi to spray the Evicel, whereas the IFU indicates that the pressure be set at 20-25 psi.

A second life-threatening case involved a patient who developed air embolism after being treated with Evicel via an air pressure device at 2 bars of pressure, during surgery for a laparoscopic partial nephrectomy. It was reported that the patient had been very stable throughout the surgery. The renal artery had been clamped prior to Evicel application. Within 2-3 minutes of application of Evicel using the gas injector to inject medical air (with the tip within 1 cm to the surface of the resected renal margin), the patient's vital signs became very unstable. It was reported that the patient made a full

and uneventful recovery with no sequelae. The reporter considered the event to be related to the excessive pressure introduced to the “air pressure device” during Evicel application.

A third case of air embolism was reported in a patient who was undergoing an open sacral mass resection. During the operation, approximately two to three minutes after Evicel use for haemostasis, the patient suddenly lost blood pressure and went into a pulseless electrical activity (PEA) rhythm. The patient developed bradycardia, abrupt loss of end-tidal CO2, and severe abrupt hypotension, and was placed in the supine position, received cardiopulmonary resuscitation (CPR) and several rounds of epinephrine. After regaining a pulse five minutes later, the patient was transferred to the intensive care unit (ICU). The surgery time was extended by 30 minutes. The patient rapidly improved and was extubated the same day. The patient was discharged from the hospital without sequelae. It was noted that Evicel was delivered via a spray applicator less than 5 cm, if not closer, from the tissue. The pressure regulator was set at 50 psi and was 100 cm from the pressured air source on the wall. The tip of the Evicel applicator was very close to a vein.

Another fatal case involved a patient who was undergoing a revision laminectomy with spinal fusion. Approaching the anterior epidural space, the surgeon encountered uncontrollable, excessive bleeding which resulted in a drop in haemoglobin from 14 to 8 mg/dl. The patient was transfused with two units of blood. After other haemostatic methods failed to stop the bleeding from the anterior epidural space, one 5-ml Evicel was dispatched to the operating theatre. A pressure regulator was used to set the pressure of the air source. The air pressure was reportedly set within the manufacturer-specified range of 15-25 psi. The actual numeric air pressure setting was not available. A "standard 6 cm tip" on the applicator device was utilized. The operating surgeon had no prior experience using Evicel or Quixil. The actual distance between the applicator tip and the bleeding surface was requested but was not reported. It was described as "closer than recommended”. The first 1 to 2 ml of Evicel was dripped onto the bleeding surface. When the bleeding continued, the remainder of Evicel (approximately 8 ml) was sprayed to the target site with "one continuous burst of pressure" in "a matter of seconds" by the surgeon using a foot paddle to apply the pressurized air.
Immediately after the Evicel spray, the patient went into cardiac arrest with pulseless electrical activity (PEA). End tidal carbon dioxide rapidly decreased.

In each case there was a failure to follow at least one of the current guidelines on administration of spray application of Evicel 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 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 Article 20 review, 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 20 review, 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 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 educational 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 Evicel spray application.

## *2.2. Risk minimisation activities*

Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan including a risk minimisation plan.

The following additional risk minimisation activities were required:

The MAH shall ensure that, at the time of the European Commission decision for this procedure (EMEA/H/C/000898/A20/0018), 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 CO2 only;
- restriction to open surgery and - if the minimum spray distance of 4 cm can be accurately judged – laparoscopy;
- correct pressure and distance from tissue depending on kind of surgery (open or laparoscopic);

- 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 ensure that, within three months of the European Commission decision on this procedure (EMEA/H/C/000898/A20/0018), all users of the spray application of this product are provided with:

- labels for the pressure regulator that inform about the correct pressures and distances in open and laparoscopic procedures;
- a warning card that informs about the correct pressures and distances for the spray application for open and laparoscopic procedures;
- 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 2 years of the European Commission decision on this procedure (EMEA/H/C/000898/A20/0018), the product can only be used with a pressure regulator that caps the maximum pressure at 1.7 bars.

Those additional risk minimisation measures have been inserted in the Annex II of the Product Information.

The MAH is requested to submit an updated version of the RMP at time of the next PSUR submission in order to properly reflect the above mentioned measures.

## *2.3. Product information*

The CHMP revised the Evicel product information in accordance with the agreed risk minimisation measures, to ensure the safe and effective use of Evicel. The major changes to the SmPC was the amendment of

In the SmPC, Section 4.2 was amended, to reflect the fact that the use of Evicel is restricted to experienced surgeons who have been trained in the use of Evicel 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 Evicel should be used with 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 Evicel spray application should only be used if it is possible to accurately judge the spray distance as recommended by the manufacturer, especially during laparoscopy. 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 Evicel should only be sprayed using carbon dioxide gas.

In the Package Leaflet, a sentence was added to Section 2 stating that Evicel 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 the Instructions for use, a sentence restricting the use of Evicel to experienced surgeons who have been

trained in the use of Evicel was added, together with a table clarifying the pressure and distance from tissue recommended by the manufacturer.

The product information has been amended in line with the latest Annex II QRD template.

# 3. Overall discussion and benefit/risk assessment

Having considered the available data, the MAH's responses and taking into account 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 safety concern of air/gas embolism associated with sprayable fibrin sealants. In particular, the MAH should 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 that spraying Evicel in endoscopic procedures should be contra-indicated.

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 Evicel by spray application should only be considered if it is possible to accurately judge the spraying distance. Spraying Evicel in endoscopic procedures should therefore be contra-indicated. For laparoscopic procedures, insufflations offers a visual field of down to 4cm and the CHMP therefore considered that the benefit-risk profile for the use of sprayable Evicel in laparoscopic procedures is the same as open surgical procedures and could be managed through the proposed risk minimisation measures. The CHMP recommended a warning to be included in Section 4.4 to reflect the fact that the Evicel spray application 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 that the use of Evicel should be restricted to experienced surgeons who have been trained in the use of Evicel. 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 Evicel because of the possibility of occurrence of air or gas embolism. The CHMP revised the Evicel PI accordingly, to ensure the safe and effective use of Evicel (see Annex I, II and IIIB).

### 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 Evicel as supportive treatment in surgery, improvement of haemostasis and suture support for haemostasis in vascular surgery, 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. Overall conclusion

The CHMP recommended the variation to the terms of the marketing authorisation for Evicel for which the revised summary of product characteristics and package leaflet are set out respectively in annexes I and IIIB of the opinion.

The scientific conclusions and the grounds for the amendment of the SmPC, Annex II and package leaflet are set out in Annex IV of the opinion.

This CHMP recommendation is subject to new conditions and requirements of the marketing authorisation with regard to the safe and effective use of the medicinal product as set out in Annex II of the opinion.

# 5. Action plan

## 5.1. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the outcome of the present review. The DHPC should be circulated to all Evicel users (Operating Room Directors, Materials Managers, surgeons using Evicel and Risk Managers at all Evicel Facilities), in all member states where Evicel is currently supplied, no later than 3 December 2012.

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

# 6. Conclusion and grounds for the recommendation

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Evicel initiated by the European Commission.
- 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 Evicel 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 Evicel 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 Evicel as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and as suture support for haemostasis in vascular surgery, is positive under normal conditions of use, subject to the implementation of the agreed risk minimisation measures, including changes to the product information.

The CHMP has therefore recommended the variation of the marketing authorisation for Evicel in accordance to the Product Information set out in annexes I and IIIB and the conditions set out in Annex II.