Annex II

Scientific conclusions and grounds for variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation

Background information

From 2008 until May 2012, a total of eight cases of life-threatening air embolism were associated with the spray application of the fibrin sealants 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 case was received 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use of Evicel and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.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 (see Annex I).

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.

On 15 November 2012, the CHMP concluded the review of Quixil (for which four cases of life-threatening 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.

The CHMP also concluded the Article 20 review on Evicel. The Committee agreed that the benefit-risk balance of Evicel was positive under normal conditions of use, subject to similar risk minimisation measures (including changes to the Product Information) as for Quixil.

This report only reflects the assessment of Tisseel/Tissucol, Artiss and Beriplast P.

Scientific Discussion

With regard to the efficacy of sprayable fibrin sealants, the CHMP assessed the available information, including data submitted by the MAHs. 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 use of fibrinogen-containing sealants in the approved indications.

Risk of air embolism associated with the spray application of fibrin sealants

With regards to safety, the CHMP noted that the main risk with sprayable fibrin sealants is the risk of air embolism, due 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 the identification of measures that would be necessary and adequate to minimise this risk.

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:

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 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 accurately judge the distance from the target tissue when spraying. As a result, gas embolism may occur even with a reduced pressure.

A single not well documented non-fatal case of a potential air embolism in association with Tisseel was reported in 2009. The patient underwent a surgical procedure for an unknown reason and Tisseel was reported to have been sprayed using the Easyspray pressure regulator to a 'closure port' leading to an air embolism. No other details were provided.

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 practice. They were of the opinion that CO_2 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 CO_2 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.

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.

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. 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.

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 regulator 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 caps the maximum pressure at 2.0 bar in open wound surgery and using a pressure regulator device that deliver a maximum pressure of 1.5 bar and carbon dioxide gas only 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 CO_2 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 CO_2), 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 CO_2 cylinders and respective pressure reducing connectors in the operating theatre. The anticipated benefit of mandating CO_2 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. Therefore the CHMP agreed 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 higher when fibrin sealants are sprayed using air, as compared to CO_2 and cannot be excluded with Tisseel/Tissucol and Artiss when sprayed in open wound surgery. In minimally invasive/laparoscopic procedures (Tisseel/Tissucol), only carbon dioxide gas should be used.

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

The CHMP agreed on a Direct Healthcare Professional Communication (DHPC), to communicate the outcome of the present review. The CHMP agreed that the DHPC should be circulated to all users of those products in Europe, no later than 15 January 2013.

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. An attachment of air feeding lines or other device components to the manual spray tips physically is not possible. The risk of air embolism with this product 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).

Benefit Risk balance

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 Professional Communication.

Beriplast P

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 gastro-duodenal 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).

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 fibrinogen-containing 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 fibrinogen-sealants 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 fibrinogen-containing 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 fibrinogen-sealants 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 Beriplast P 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.