Annex II

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

Scientific conclusions

Overall summary of the scientific evaluation of Quixil

Background information

Quixil is a first generation fibrin sealant containing two components, human clottable protein and human thrombin and was approved via the mutual recognition procedure with the UK as reference member state.

The fibrinogen component of Quixil also contains tranexamic acid. Quixil is indicated as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. It 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.

From 2008 until May 2012, four cases of life-threatening air embolism were reported for the 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use of Evicel and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.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.

Scientific Discussion

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 use of Quixil in the approved indications.

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 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. 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 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 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 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.

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 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.

The MAH also 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 the Quixil spray application.

In conclusion, 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 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 authorities 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 with a pressure regulator that caps the maximum pressure at 2.5 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 CO_2 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). Minor formatting changes were also introduced.

Finally, the CHMP agreed on a Direct Healthcare Professional Communication (DHPC), 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 in France and Italy, no later than 30 November 2012.

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 III), together with the agreed risk minimisation measures (see Annex IV) and the agreed Direct Healthcare Professionals Communication.

Grounds for the variation to the terms of the marketing authorisation

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.