Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations and detailed explanation for the differences from the PRAC recommendation

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations subject to conditions and detailed explanation for the differences from the PRAC recommendation

The CMDh considered the below PRAC recommendations following the procedure under Article 107i of Directive 2001/83/EC dated 10 October 2013 with regards to Hydroxyethyl starch containing medicinal products solutions for infusion:

1. Overall summary of the scientific evaluation of solutions for infusion containing hydroxyethyl starch medicinal products by PRAC

Hydroxyethyl starch (HES) solutions for infusion include products with starch derived from potato or corn with different molecular weights and substitution ratios. HES containing solutions for infusion were indicated mainly for the treatment and prophylaxis of hypovolaemia and hypovolemic shock.

HES solutions have been the object of two reviews. The first review was initially started under the framework of Article 31 of Directive 2001/83/EC. The PRAC issued a recommendation on available data for this review in June 2013, concluding that HES solutions should be suspended in all patient populations. Following requests for re-examination by marketing authorisation holders (MAHs), the PRAC confirmed its previous position under the Article 31 in October 2013. While the re-examination was ongoing some Member States decided to suspend or limit the marketing or use of these medicines in their territories. In accordance with the EU legislation, this type of action required that an EU review procedure be carried out. Consequently, a second review of HES solutions under Article 107i of Directive 2001/83/EC was initiated, and it ran separately but in parallel with the re-examination of the Article 31, also finalising in October 2013. However, it must be noted that new evidence was considered in the procedure under Article 107i of Directive 2001/83/EC. This new evidence was not available when the PRAC recommendation on the procedure under Article 31 of Directive 2001/83/EC was issued in June 2013 and could therefore not be considered in the re-examination of the latter in October 2013. It is on the basis of the totality of the data available, including the new evidence, that the PRAC issued conclusion on the procedure provided for in Article 107i of Directive 2001/83/EC in October 2013. Therefore the conclusions on the Article 107i of Directive 2001/83/EC reflect the most complete and up-to-date evaluation of the available data relating to the HES containing medicinal products.

Details of this recommendation are presented hereafter.

Under the framework of Article 107i of Directive 2001/83/EC, the PRAC considered recommendations on HES rendered in the referral under Article 31 of Directive 2001/83/EC and also reviewed available data including clinical studies, meta-analyses of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, spontaneous reports on the safety and efficacy of hydroxyethyl starch containing products for solutions for infusion, as well as stakeholders' submissions in particular with regards to the risk of mortality and renal failure.

On the basis of the available data, in particular results from VISEP, 6S and CHEST studies, the PRAC concluded that HES is associated with an increased risk of mortality and renal failure in patients with sepsis, in critically ill and burn patients and that the benefits of HES do not outweigh the risks in these patient populations.

However, it was noted that short-term haemodynamic improvements have been observed in other patient populations, including surgical and trauma patients. Whilst recognising the limitations of these studies which included limited size and short duration of follow-up, the PRAC noted that some volume

sparing effect was reported in Madi-Jebara *et al.* 2008, that suggested that HES 130/0.4 6% seems to have benefits over twice the volume of Ringer's lactate in preventing spinal anaesthesia induced hypotension. Some benefit for elective surgical patients has also been shown in short-term surrogate hemodynamic outcomes along with a modest volume sparing effect (Hartog *et al*. 2011). In hypovolaemic patients with normal pulmonary function, the use of colloids to maintain colloid-osmotic pressure may limit the development of peripheral as well as pulmonary oedema (Vincent JL 2000). Some publications also suggest that colloids might help to prevent positive fluid balance and/or over-infusion of fluids (Wills 2005, Naing CM and Win DK 2010). Some of authors argue that a positive net fluid balance is associated with a decrease in organ perfusion and an increased mortality (e.g. Sadaka F *et al*. 2013, Payen D *et al*. 2008). Meybohm P *et al*. 2013 suggest that use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. Martin *et al* 2002 showed that HES treatment resulted in a significantly lower estimated blood loss and that there was no difference in red blood cells, or blood product utilisation among the groups. Hamaji et al 2013 also showed that significantly fewer red blood cell transfusions were required in the HES group.

Therefore, the PRAC noted the available data from studies in surgical and trauma patients and considered that although these studies were limited in size and duration of follow-up they did provide some reassurance that the risks of mortality and renal injury in surgical and trauma patients may be lower than those in the critically ill and sepsis patients. Although the mechanisms by which increased renal injury and mortality occur is not well established, it is possible that the degree of inflammatory processes seen in sepsis and critically ill patients is greater and associated with significant capillary leakage compared with other patient populations such as the perioperative setting after elective surgery or un-complicated trauma where the systematic inflammatory process and the extent of capillary leak may be lower.

New results from CRYSTAL have also become available. Despite the studies' limitations which were noted, the results from the CRYSTAL study comparing colloids to crystalloids showed that in patients with hypovolaemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this requires further investigations. In addition, in the BaSES study, the hospitalisation time was significantly reduced in patients treated with 6% HES 130/0.4 compared to 0.9% NaCl. Results from the RaFTinG registry in intensive care units, an observational, non-randomised study aiming to gather more information in 'real-life' clinical practice showed no statistically significant differences between patients treated with crystalloids only (n=2482) and those treated with colloids (all HES preparations and gelatin, n=2063) for the endpoints of 90-day mortality. The PRAC therefore acknowledged the results of this studies which shows no risk of mortality associated with the use of HES but considered that given the limitations of this study its findings could not negate the findings from 6S and VISEP studies that had shown an increased risk of mortality in critically ill patients.

Additional expert advice was sought from an ad-hoc expert group. The experts agreed that the benefits may be observed in severe hypovolaemia in short duration only at the beginning i.e. perioperative setting and disappearing faster with patient's stabilisation. The experts suggested that benefit of HES may be seen in particular in perioperative bleeding.

Therefore, the PRAC agreed that the therapeutic indication of hydroxyethyl starch containing products should be restricted to treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. However additional measures must be implemented to minimise potential risks in these patients. HES solutions should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. The posology section should identify the maximum daily dose and should recommend that the lowest possible effective dose should be employed. HES products are contraindicated in patients with renal impairment or renal replacement therapy but the contraindications should also be extended to include other patient populations including patients with

sepsis, critically ill patients and burns patients. The PRAC considered that the use of HES must be discontinued at the first sign of renal injury. Monitoring of renal function in patients is recommended for at least 90 days. Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders. The product information will be updated to reflect these restrictions and warnings.

In addition, two phase IV randomised clinical trials with an appropriate control and clinically meaningful endpoints will need to be conducted to provide more evidence on the efficacy and safety, including the risk of 90-day mortality and renal failure, in perioperative and trauma populations. An European drug utilisation study will also be conducted to evaluate the effectiveness of the recommended risk minimisation measures. Protocols and results of these studies will be submitted to national competent authorities according to agreed timelines. The MAHs are also encouraged to submit risk management plans to national competent authorities.

Benefit risk balance

In view of the totality of the evidence available in the procedure under Article 107i of Directive 2001/83/EC, the PRAC considered that Hydroxyethyl starch should be restricted to the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient subject to agreed restrictions, contraindications, warnings, other changes to the product information and additional risk minimisation measures.

The PRAC conclusion in the context of the referral procedure under Article 107i of Directive 2001/83/EC included additional data that was not available when the PRAC issued its recommendation on the referral in accordance with Article 31 of Directive 2001/83/EC in June 2013 and therefore could not be considered in the re-examination of the latter in October 2013. Therefore the conclusions on the Article 107i of Directive 2001/83/EC reflect the most complete and up-to-date evaluation of the available data relating to the HES containing medicinal products.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 107i of Directive 2001/83/EC, for hydroxyethyl starch containing products for solutions for infusion.
- The PRAC noted the conclusions of a review under article 31 of Directive 2001/83/EC. However, for the current procedure under Article 107i of Directive 2001/83/EC the PRAC reviewed new available data, with a focus on risk of mortality and renal failure, including clinical studies, meta-analyses of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations and stakeholders' submissions.
- The PRAC considered that the use of hydroxyethyl starch is associated with an increased risk of mortality and renal replacement therapy or renal impairment in patients with sepsis, critically ill and burn patients.
- The PRAC considered, in view of the new evidence which includes data from clinical trials, further expert advice, new proposals for additional risk minimisation measures, including restrictions on use and a commitment from the MAHs to perform additional studies in patients with trauma and in elective surgery, that the benefit of hydroxyethyl starch containing products outweighs the risk in the treatment of hypovolaemia due to acute blood loss when

crystalloids alone are not considered sufficient. This is subject to restrictions, warnings and other changes to the product information.

- The PRAC concluded that hydroxyethyl starch containing products should be contraindicated in patients with sepsis, in critically ill and burn patients. In addition, special warnings in surgery and trauma patients have been included.
- The PRAC also concluded that there was need for further risk minimisation measures such as information to patients and healthcare professionals. Core elements of a direct healthcare professional communication were agreed, together with the timelines for distribution, and that studies should be conducted. The PRAC also considered that studies should be conducted to provide more evidence on the efficacy and safety of hydroxyethyl starch in the perioperative setting and trauma.

The PRAC concluded that the benefit-risk balance for hydroxyethyl starch containing medicinal products remains favourable in treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient subject to the agreed restrictions, contraindications, warnings, other changes to the product information and additional risk minimisation measures.

The PRAC conclusion in the context of the referral procedure under Article 107i of Directive 2001/83/EC included additional data that was not available when the PRAC issued its recommendation on the referral in accordance with Article 31 of Directive 2001/83/EC in June 2013 and therefore could not be considered in the re-examination of the latter in October 2013. Therefore the conclusions on the Article 107i reflect the most complete and up-to-date evaluation of the available data relating to HES containing medicinal products.

2. Detailed explanation for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, with regards to the two phase IV randomised clinical trials (RCTs) requested to provide more evidence on the efficacy and safety in perioperative and trauma populations, including the risk of 90-day mortality and renal failure, , the CMDh encouraged the MAHs to jointly submit common study protocols. To this end the MAHs were strongly advised to seek scientific advice with the European Medicines Agency, in time for the submission of the study protocols to the national competent authorities (NCAs) within 6 months of the European Commission Decision. Consequently the CMDh decided that synopsis were not required in advance of the recommended scientific advice.

The CMDh amended the due date for the submission of the protocol of the drug utilisation study which is now also due within 6 months of the European Commission Decision in order to harmonise submission dates of all conditions.

In view of the above and considering that the study protocols of the drug utilisation study and of the two randomised clinical trials are conditions to the marketing authorisation, the CMDh noted that these elements should be reflected in a risk management plan. Companies had been encouraged to submit core elements of the risk management plan, but the CMDh considered that this should be a condition. The MAHs should submit within 6 months of the European Commission Decision, the core elements (including protocol of DUS, protocols of the RCTs) of a risk management plan in EU format and this was included in Annex IV.

The CMDh also considered that the direct healthcare professional communication (DHPC) should be submitted to the NCAs where HES products are marketed, within one week of the CMDh adopted position as per agreed communication plan.

CMDh position

The CMDh having considered the PRAC recommendation dated 10 October 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC and the oral explanations by the Marketing Authorisation Holders on 21 October 2013, reached a position on the variation to the terms of the marketing authorisations of Hydroxyethyl starch solutions for infusion containing medicinal products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.