Annex II

Scientific conclusions and CMDh's detailed explanation on the scientific grounds for differences with the PRAC recommendation

Scientific conclusions

In 2013, following a review of the risk of kidney injury and mortality related to hydroxyethyl starch (HES) solutions for infusion when administered in patients with sepsis or critical illness, the Pharmacovigilance and Risk Assessment Committee (PRAC) recommended risk minimisation measures such as restrictions in use of these medicinal products. PRAC also recommended a drug utilisation study to evaluate the effectiveness of these risk minimisation measures.

Results from two drug utilisation studies, submitted by the concerned Marketing Authorisation Holders ('MAHs') in 2017, have shown that the recommended restrictions in use are not being sufficiently adhered to.

On 17 October 2017, Sweden triggered an urgent Union procedure under Article 107i of Directive 2001/83/EC, and requested the PRAC to assess the impact of the above non-adherence to the product information on the benefit-risk balance of hydroxyethyl starch (HES) solutions for infusion and issue a recommendation on whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 11 January 2018 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Hydroxyethyl starch (HES) solutions for infusion contain starch with different molecular weights (mainly 130kD; 200kD) and substitution ratio (the number of hydroxyethyl groups *per* glucose molecule). HES solutions for infusion are authorised worldwide for the treatment of hypovolaemia associated with various conditions.

In 2012 and 2013, PRAC reviewed the benefits and risks of HES solutions for infusion in the treatment and prophylaxis of hypovolaemia, within Article 31[1] and 107i[2] referral procedures. These reviews were triggered by the results from large randomised clinical studies[3,4,5] which showed an increased risk of mortality in patients with sepsis and an increased risk of kidney injury requiring dialysis in critically ill patients following treatment with HES solutions for infusion.

As result of the reviews, the PRAC recommended that use of HES solutions for infusion should be restricted to the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. The PRAC also contraindicated the use of HES solutions for infusion in patients with sepsis or who are critically ill. Furthermore, the PRAC requested that, as conditions to the marketing authorisations of these medicinal products, further studies should be carried out on the use of these medicines in elective surgery and in trauma patients. The PRAC also required that drug utilisation should be studied to evaluate the effectiveness of the risk minimisation measures. The focus for the drug utilisation studies (DUSs) has been to evaluate the adherence to the restrictions in use, implemented in the product information, concerning the indication, posology, and contraindication for HES solutions for infusion.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starch-containing_solutions/human_referral_prac_000012.jsp&mid=WC0b01ac05805c516f
[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starch-containing_medicines/human_referral_prac_000029.jsp&mid=WC0b01ac05805c516f
[3] Perner A, Haase N, Guttormsen AB et al. Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. N Engl J Med 2012;367(2):124-34
[4] Brunkhorst FM, Engel C, Bloos F et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. N Engl J Med 2008; 358(2):125-39
[5] Myburgh J, Finder S, Bellomo R *et al*. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367:1901-11

On 5th July 2017 and 9th October 2017, results from two DUSs on the effectiveness of the implemented risk minimisation measures have become available. These include drug utilisation data from 11 EU Member States. These data raise serious concerns as they showed use of HES solutions for infusion in patient populations which are contraindicated such as those who are critically ill, or with sepsis[3,4,5]. In light of the well-established risk for serious harm when HES solutions for infusion are used in patients with critical illness, including sepsis, together with the above-mentioned newly available data, Sweden triggered, on 17th October 2017, an urgent Union procedure under Article 107i of Directive 2001/83/EC. Due to the serious public health impact, Sweden was considering suspending the marketing authorisations for the above mentioned medicinal products, and therefore requested an urgent review of the matter at the European level, and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of HES solutions for infusion and issue a recommendation on whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

In its assessment, the PRAC considered the totality of evidence which includes all newly available data since the previous referral procedures, including results from DUSs, clinical studies, meta-analyses of clinical studies, post-marketing experience, Eudravigilance data, literature review, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations as well as stakeholders' submissions and views expressed by experts during an ad-hoc experts meeting, taking into account also the characterisation of benefits and risks concluded in the previous referral procedures.

The PRAC also considered views from individual PRAC members on the benefit/risk balance of HES solutions for infusion as well as on the use of these products at the national level. These views are based on PRAC members' routine review processes and preparation. These views, along with all substantial data and information crucial for the full understanding of these views have been either shared with all the parties involved or otherwise made available in the course of the procedure.

With regards to efficacy, PRAC considered that there is no new significant information related to the approved indication. Overall, the evidence for this indication is based on studies for which the sample size and the duration of follow-up are limited. Is it also noted that although the benefit has been demonstrated in terms of a volume-sparing effect, and there is some support for short-term hemodynamic effects, it remains uncertain to what extent this translates into more patient-relevant outcomes. The benefits in the approved indication therefore remain modest.

With regards to the safety data related to these products, the PRAC reviewed all available evidence since the last referral and concluded that the previous conclusions that HES solutions for infusion is associated with an increased risk of mortality and renal failure in patients with sepsis or critical illness were confirmed and that the available information, including more recently submitted clinical data, do not change the established risk in these patient populations.

Treatment of hypovolemia should replace lost blood volume in order to restore tissue perfusion and oxygenation to ultimately prevent renal injury and death. There is a direct relation between the degree of hypovolemia and the risk for renal injury and death. A more pronounced hypovolemia requires a greater volume (dose) of HES solutions for infusion and is also associated with a greater risk for renal injury and death. Consequently, a direct correlation is to be expected between the indication for treatment with HES solutions for infusion, the dose of HES solutions for infusion required and with the risk for renal injury and death. It should also be noted that the ultimate benefit expected from HES solutions for infusion (and treatment of hypovolemia in general) is a reduction of mortality and lower incidence of renal failure. The safety concerns of primary importance in this referral are increased mortality and a higher incidence of renal failure – the opposite of the benefit expected.

Amongst other data related to safety, the PRAC reviewed the results from two separate DUSs conducted to assess the effectiveness of the risk minimisation measures imposed as an outcome of the 2013 referral, and concluded that these studies despite a potential limitation of possible misclassification, are representative of the clinical usage in the European Union and that key results are reliable. The results indicate that the implemented restrictions in use are not sufficiently adhered to. Overall non-adherence to the revised product information was reported to be high, and PRAC was particularly concerned that approximately 9% of patients exposed to HES solutions for infusion were critically ill, approximately 5-8% of patients had renal impairment and approximately 3-4% of patients had sepsis.

In view of the overall exposure to HES solutions for infusion in the EU, estimated to about 1.5 to 2 million patients per year since 2014 and the reported extent of usage in patients with sepsis from the two DUSs, the estimated level of continued usage in populations where serious harm has been demonstrated raises important public health concerns, including a potentially increased mortality.

The PRAC considered other further risk minimisation measures to sufficiently minimise this exposure, including changes to the product information, direct health care professional communication, educational materials, warning on the primary container of the products, sign-in for medication form, prescription sheet/checklists. However, the available evidence shows that the non-adherence is not only due to a lack of awareness of the restrictions by prescribers but also due in some cases to deliberate choice, rendering further communication and education unlikely to be sufficiently effective to address the risks identified. The medication form/checklists would also raise feasibility issues in an emergency setting. Proposals to amend the indications and contraindications were not considered sufficient to have a significant impact on prescriber behaviour. The PRAC also noted that the current clinical experience suggests that it is difficult to clearly separate patient populations where randomised clinical trials have shown serious harm from populations targeted by the approved indication. Patients in the approved indication may become critically ill or septic shortly after receiving HES solutions for infusion and these patients cannot be identified prospectively. This complicates effective risk minimisation in these patients.

The PRAC concluded that no additional risk minimisation measures to ensure safe and effective use of HES solutions for infusion would be effective or feasible in a reasonable timeframe, where important number of patients at high risk would continue to be exposed.

The PRAC also consulted an ad-hoc expert group and considered carefully views expressed during the meeting that took place on 18 December 2017. The PRAC duly considered the view of the majority of the experts in the meeting that HES is used in clinical practice. The PRAC also noted the view of an expert concerning shared clinical experience in handling cases in a EU Member State where HES solutions for infusion are little used and where no medical need is raised.

This reflects a long-standing controversy among health-care professionals and echoes the range of stakeholder responses received in the current review.

Overall, taking into account the divergences amongst the experts on some important issues, the position from the PRAC members on the national situation regarding the clinical use of these products and the stakeholders submissions, PRAC did not consider the clinical utility of these products to outweigh the risk of mortality and renal failure to the proportion of patients with critical illness or sepsis that continue to be exposed to HES solutions for infusion.

In view of the seriousness of the safety issues and that the proportion of patients who are exposed to these risks in the absence of effective risk minimisation measures could have important public health consequences including a potentially increased mortality, the PRAC concluded that the benefit risk

balance of hydroxyethyl starch solutions for infusion is no longer favourable and recommended the suspension of the marketing authorisations.

The PRAC noted that the clinical studies imposed following previous referrals procedures (TETHYS and PHOENICS) to characterise the efficacy and safety in trauma and elective surgery, which is currently the target population for which the product is indicated are ongoing.

Having reviewed the PRAC recommendation[6], the CMDh agreed by a majority on 24 January 2018 with the PRAC overall conclusions and grounds for recommendation. The position was afterwards forwarded to the European Commission, the Member States, to Iceland and Norway and to the marketing authorisation holders for the above mentioned medicinal products, together with its annexes and appendices.

Revision of PRAC recommendation

During the decision-making process, at a meeting of the Standing Committee on Medicinal Products for Human Use, some EU Member States raised new questions of technical nature which they considered had not been sufficiently addressed in the PRAC recommendation and CMDh position. In light of this, the PRAC recommendation and CMDh position were referred back to the Agency by the European Commission for further consideration of any possible unmet medical need that could result from the suspension of the marketing authorisations for the medicinal products concerned by the referral, as well as the feasibility and likely effectiveness of additional risk minimisation measures.

The PRAC discussed the above two points at its May meeting, taking into consideration information provided by the Member States.

The PRAC has considered all elements expressed in relation to the impact of a suspension of the marketing authorisation for HES solutions for infusion on a potential unmet medical need at national level, including comments submitted by the MAHs in writing and at oral explanations, responses from Member States and other stakeholders' views.

With regard to the impact on a suspension of the marketing authorisations for HES solutions for infusion, fifteen EU Member States and Norway mentioned that no unmet medical need is expected in case of suspension of the marketing authorisations for HES solutions for infusion.

The PRAC carefully considered all the information provided in relation to a potential unmet medical need at national level should the marketing authorisations for HES solutions for infusion be suspended. Eight EU Member States have mentioned that a suspension of the marketing authorisations for HES solutions for infusion would have an impact in the national clinical practice as HES solutions for infusion fulfils currently a medical need in their territory. The PRAC considered that despite arguments raised by some Member States, the potential for unmet medical need is not established. Most of the arguments refer to the use of HES solutions for infusion outside the terms of the MA or to claimed benefits that are not clinically significant or supported by robust data.

The PRAC concluded that the claimed clinical utility for these products does not outweigh the risk of mortality and renal failure to the proportion of patients with critical illness or sepsis that continues to be exposed to HES solutions for infusion.

The PRAC have also further considered for the feasibility and likely effectiveness of risk minimisation measures.

[6] PRAC Recommendation EMA/PRAC/1707/2018 Corr.1 and PRAC AR EMA/PRAC/808891/2017 Corr.1

The PRAC considered further risk minimisation measures which could potentially sufficiently minimise this exposure, including restricted access / distribution to hospitals and physicians, changes to the product information, direct health care professional communication, educational materials to be distributed in cooperation with some learned societies, warning on the primary container of the products, medication form and follow-up questionnaire. However, the available evidence shows that the non-adherence is not only due to a lack of awareness of the restrictions by prescribers but also due to deliberate choice, rendering further communication and education unlikely to be sufficiently effective to address the risks identified. A restricted distribution system to accredited hospitals or physicians would raise serious feasibility concerns and would be unlikely to be effective considering the particular type of distribution and usage of HES solutions for infusion. A medication form to be filled before administration would also raise feasibility issues in an emergency setting. A follow-up questionnaire to be filled after administration would not be effective in minimising the risk. Proposals to amend the indications and contraindications were not considered have a sufficient impact on prescriber behaviour and were not supported by appropriate scientific evidence.

In conclusion, no risk minimisation measures or combination of measures have been identified which would be sufficiently effective or feasible to implement in a reasonable timeframe, when an important number of patients at high risk for serious harm, would continue to be exposed.

In the light of the above information, the PRAC confirmed at its May 2018 plenary meeting, its previous scientific conclusions that the benefit risk of HES solutions for infusion is negative and recommended to suspend the marketing authorisations of these medicinal products.

Revised 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 (HES) solution for infusion (see Annex I).
- The PRAC reviewed all newly available data, including results from Drug Utilisation Studies (DUS), clinical studies, meta-analyses of clinical studies, post-marketing experience, Eudravigilance data, literature review, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, stakeholders' submissions and views expressed by experts during an ad-hoc experts meeting. The PRAC also reviewed responses from Member States in relation to the potential unmet medical need and proposals for additional risk minimisation measures.
- With regards to the efficacy, PRAC considered that there is no new significant information related to the approved indication. Overall, the evidence for this indication is based on studies for which the sample size and the duration of follow-up are limited. Is it also noted that although the benefit has been demonstrated in terms of a volume-sparing effect, and there is some support for short-term hemodynamic effects, it remains uncertain to what extent this translates into more patient-relevant outcomes. The benefits in the approved indication therefore remain modest.
- With regards to the two separate DUSs conducted to assess the effectiveness of the risk minimisation measures imposed as an outcome of the 2013 referral, PRAC concluded that these studies, despite limitations due to possible misclassification, are representative of the clinical usage in the European Union and that key results are reliable. The results indicate that

the implemented restrictions in use are not adhered to. Overall non-adherence to the revised product information was reported to be high, and PRAC was particularly concerned that approximately 9% of patients exposed to HES solutions for infusion were critically ill, approximately 5-8% of patients had renal impairment and approximately 3-4% of patients had sepsis.

- The PRAC conclusions of previous reviews under Article 31 of Directive and Article 107i of Directive 2001/83/EC were that HES solutions for infusion are associated with an increased risk of mortality and renal failure in patients with sepsis or critical illness. PRAC confirmed that the available information, including more recent submitted clinical data, do not change the established risk of increased mortality and renal failure related to the use of HES solutions for infusion in these patients. The new data provided does not change the conclusions from the previous 2013 referral that the benefits of HES solutions for infusion do not outweigh the serious risks in patients with sepsis or critical illness.
- The PRAC also noted the overall exposure to HES solutions for infusion in the EU, estimated to about 1.5 to 2 million patients *per* year since 2014. In view of this exposure and the results from the two DUSs, the PRAC concluded that the estimated level of continued usage in populations where serious harm has been demonstrated raises important public health concerns, including a potentially increased mortality.
- The PRAC further acknowledged that the current clinical experience suggests that it is difficult to clearly separate patient populations where randomised clinical trials have shown serious harm from populations targeted by the approved indication. Patients in the approved indication may become critically ill or septic shortly after receiving HES solutions for infusion and these patients cannot be identified prospectively. This complicates effective risk minimisation in these patients.
- Furthermore, the PRAC considered options for measures to further mitigate these risks, including changes to the product information, direct health care professional communication, educational materials, warning on the primary container of the products, sign-in for medication form, prescription sheet/checklists, restricted access and distribution system to accredited hospitals/physicians. However, the available evidence shows that the non-adherence is not only due to a lack of awareness of the restrictions by prescribers, rendering further communication and education unlikely to be sufficiently effective. The medication form/checklists would also raise feasibility issues in an emergency setting, and implementation of a restricted access/distribution program is unlikely to be feasible and sufficiently effective across EU Member States considering the particular type of distribution and usage of HES solutions for infusion and some national limitations. The PRAC concluded that no additional risk minimisation measure or combination of risk minimisation measures, to sufficiently ensure safe and effective use of HES solutions for infusion could be identified.

In view of the above, the PRAC concluded that pursuant to Article 116 of Directive 2001/83/EC the risks related to the use of HES outweigh their benefits and thus the benefit-risk balance of HES solutions for infusion is no longer favourable.

Therefore, the PRAC recommends the suspension of the marketing authorisations for all medicinal products referred to in Annex I.

For lifting the suspension, the MAHs should provide reliable and convincing evidence on a favourable benefit risk balance in a well-defined population, with feasible and effective measures to adequately minimise exposure of patients at an increased risk of serious harm.

Revised CMDh position

Having reviewed the revised PRAC recommendation[7], the CMDh disagreed with the PRAC overall conclusions and grounds for recommendation.

Detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CMDh took into consideration the revised PRAC recommendation to suspend the marketing authorisations for solutions for infusion adopted at May PRAC plenary meeting. The CMDh took also into consideration the responses to the questions raised by the European Commission and the elements collected by the PRAC, as well as the information provided by the MAH during the oral explanations held on 28 May 2018 and 25 June 2018.

- ***Impact on the clinical practice of potential suspension of MA for HES solutions for infusion***

The benefit of HES solutions for infusion has been demonstrated in terms of volume-sparing effect, and there is some support for effects on short-term hemodynamic effects, although there is some uncertainty to what extent this translates into more patient-relevant outcomes.

A positive benefit-risk balance has been established in elective surgery and trauma patients. As an outcome of the 2013 referral, post-authorisation studies were imposed to the MAHs in these clinical settings and are a condition to the terms of the MAs for HES solutions for infusion. These studies as well as on-going voluntary clinical studies (e.g. FLASH study) would further characterise the efficacy and safety profile in elective surgery and trauma patients. The CMDh emphasised the importance of having meaningful results from these studies as soon as possible. The CMDh noted the PRAC conclusions that no new safety data was provided that would change the conclusions on the safety profile established in the previous referrals for HES solutions for infusion.

The CMDh also noted that treatment characteristics in some of the previously assessed clinical studies such as strength, dose or length of treatment may differ from current practice.

The CMDh considered also the divergence of positions of the learned societies in the EU. The European Society of Anaesthesiology and some national learned societies, stated that HES solutions for infusion play a role in the therapeutic armamentarium of hypovolemic shock in patients who cannot be stabilised with crystalloids alone. On the contrary, the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) and five Scandinavian learned societies supported the suspension of the marketing authorisations for HES solutions for infusion.

These views often reflected the current national medical practice and the debate in the medical community.

The CMDh acknowledged the complexity of managing patient suffering from hypovolemia due to an acute blood loss, and the fact that these patients require an individual evaluation. It was also considered that HES solutions for infusion are used for the treatment of life-threatening medical conditions.

The CMDh took into consideration all the new elements available since the previous CMDh position. In particular, the CMDh noted the results of a consultation of Member States where the suspension of the

[7] PRAC Recommendation EMA/PRAC/1707/2018 Rev.1 and PRAC AR EMA/PRAC/808891/2017 Rev.1 Corr.1

marketing authorisation for HES solutions for infusion would have an impact on the clinical practice where HES is reported as an adequate therapeutic option.

The CMDh noted that eight EU Member States have shared concerns about a medical need created in case of suspension of the marketing authorisation for HES solutions for infusion. Whilst some concerns related to the use of these products in clinical settings not covered by the terms of the MA, the CMDh acknowledged concerns on the medical need related to the authorised use and therefore should be taken into account, even if it might be rare.

- ***Proposals for additional risk minimisation measures and pharmacovigilance activities***

The CMDh discussed whether measures to mitigate the risks associated with HES solutions for infusion, including in particular the risk of increased mortality and renal failure in critically ill patients and patients with sepsis would be effective and feasible, taking into account new elements provided by the MAHs and Member States. In particular, the CMDh took into consideration the additional details from the MAHs on the proposed controlled access program.

The CMDh is of the position that the proposed additional measures described below would be feasible and effective to sufficiently minimise the risks by increasing awareness of HCPs, as well as ensuring that access to HES solutions for infusion is reserved to HCPs that have received adequate training.

1. Amendments to be included in the product information

The DUSs results showed that approximately 9% of patients exposed to HES solutions for infusion were critically ill, approximately 5-8% of patients had renal impairment and approximately 3-4% of patients had sepsis. It is proposed to mention explicitly in the new warnings ‘renal impairment’ in addition to ‘sepsis’ and ‘critically ill patients’; this would add further emphasis on this specific critically ill patients.

> *(1) Addition of the following warning on the outer packaging and the immediate packaging: “Do not use in sepsis, renal impairment, or critically ill patients. See all contraindications in the SmPC.”*

The CMDh acknowledged that the prescribers would not often administer the solution and therefore could not see this warning label. However, this measure should be seen as part of the complete program of risk minimisation measures. Hence:

- This measure will act as a reminder at time of administration, which is important in an emergency setting. It will complement other measures such as training to HCPs.
- It will allow targeting HCPs in charge of the administration of the medicinal product who have an important role in ensuring adherence to the adequate use of HES solutions for infusion.
- The continued presence of this warning on the packaging will also contribute to long-term awareness of HPCs.
- A reference to section 4.3 of the SmPC will avoid undermining the importance of other contraindications, and ensure these continue to be adhered to.

In terms of readability, the warning should be strongly emphasised (e.g. capitalized, bold letters or use of colours). The warning and its visual details should be subject to a user test in line with the

"Guideline on the Readability of the labelling and package leaflet on medicinal products for human use", to be submitted within 1 month from the Commission Decision.

(2) Addition of a prominent warning at the top of the SmPC and PL.

In order to prompt the attention of the recipients of the product information on the clinical situations above described, a warning to not use HES solutions for infusion in septic, renal impaired and critically ill patients should be mentioned at the top of the SmPC and PL.

2. Controlled access program

The objective of such program is to ensure the delivery of HES solutions for infusion to only hospitals/centres where HCPs expected to prescribe or administer (hereinafter 'relevant HCPs') have been trained adequately on the appropriate use of HES solutions for infusion, irrespective of the department(s) where they operate,.

The CMDh noted the concerns raised by PRAC on some models of controlled access program for HES solutions for infusion, in particular regarding feasibility due to the difficulty to define relevant prescribers / departments / hospitals and their effectiveness.

The CMDh through its representatives of NCAs have further discussed the national specificities of the healthcare systems and was of the view that the proposed controlled access program is likely to be feasible for the following reasons:

- Whilst patients eligible to treatment with HES solutions for infusion cannot be restricted to specific hospitals or hospital departments, it is possible to identify within a hospital/centre the relevant HCPs who would be prescribing/administrating HES solutions for infusion.
- The emergency setting in which the products are used does not impede the implementation of a controlled access program based on the delivery of appropriate training to the relevant HCPs as the educational program can be organised and delivered well in advance of the use of the products.
- Whilst acknowledging the difficulties of continuous training, centralising such organisation and monitoring by the MAH will address the challenges raised.

Therefore, the CMDh is of the position that each MAH shall be responsible for the implementation and the supervision of the access controlled program as follows:

- The MAH should develop the training materials for relevant HCPs expected to prescribe / administer HES solutions for infusion and agree the exact content and format of these materials with the relevant national competent authorities.
- The MAH should deliver the training on the appropriate use of HES solutions for infusion to relevant HCPs on a regular basis, as agreed with the national competent authorities. The MAH should also ensure these HCPs are provided with the following:
    - The Summary of product characteristics,
    - Training materials.
- The MAH should manage the accreditation of the hospitals / centres, ensuring that all relevant HCPs intended to prescribe/ administer HES solutions for infusion have been adequately trained. This includes recordings of trainings and accreditation.

- The MAH should ensure that HES solutions for infusion are only delivered to accredited hospitals/centres.

The above training materials should be based on the following key elements:

- the risks related to the use of HES solutions for infusion outside the terms of the MA,
- a reminder of the indication, dose, duration of treatment and contraindications and the need to comply with the product information,
- the new additional risk minimisation measures,
- the results from the DUSs.

The training materials should be based on interactive learning tools in order to ensure the active involvement of the HCPs.

The training materials should be distributed to all relevant HCPs intended to prescribe/administer HES solutions for infusion (e.g. anaesthiologists, intensive care physicians, nurses…).

In order to optimise the uptake by HCPs and their adherence to the adequate conditions of use of HES solutions for infusion, the learned societies should be involved in the development and distribution of such training materials.

The final training materials, including communication media and distribution modalities should be agreed with the National Competent Authorities.

The CMDh finally encouraged the integration of the training activities abovementioned in the continuing medical education at national level.

In view of the above and whilst noting the PRAC's reservations on the expected effectiveness of this measure, notably in view of the non-adherence by prescribers not only due to a lack of awareness, the CMDh considered that:

- The assumption that the non-adherence is not only due to lack of awareness is not supported by sufficient evidence and might not be representative of a significant portion of the prescribers population.
- This controlled access program is a key measure to ensure adherence of HCPs to the terms of the MA by increasing both the awareness of the relevant HCPs to the risks associated to the use of HES solutions for infusions and ensuring that they have received appropriate training before they can use HES solutions for infusion. It is expected that the involvement of the learned societies will have an important role in channelling the messages of the training. The effectiveness of this measure should be considered in combination with other measures.
- This measure will ensure long term effectiveness through reminders sent to the trained HCPs and training of new ones. The frequency of the training / reminders should be discussed at national level taking consideration particularities of each national healthcare system.
- In view of the seriousness of the risks related to the use of HES solutions for infusion outside the terms of the MA, the CMDh considered this measure as proportionate.

In conclusion, the CMDh is of the position that a controlled access program is feasible and likely to be effective to minimise the risk, in combination with other risk minimization measures.

This controlled access program should be described in a Risk Management Plan which shall be submitted to the National Competent Authorities for assessment within 3 months from the Commission Decision.

The details of the controlled access program, the modalities of its implementation and the final training materials, including communication media and distribution modalities should be agreed with the National Competent Authorities.

Having considered the specificities of the national systems and the need for agreement with the national competent authorities on the details on the implementation of the controlled access and the time required to complete the adequate training to all HCPs intended to use HES products and the accreditation of the hospitals/ centres, the CMDh requested that the controlled access program should be effectively implemented at the latest 9 months after Commission Decision.

3. Communication measures

Acknowledging the need of increasing the compliance to the indication and contraindications, the CMDh is of the position that a targeted communication through DHPC would be effective to this aim.

Indeed, the CMDh noted the results of the DUSs whereby there was adherence to some of the key restrictions of use recommended following the 2013 referrals (i.e. the maximum daily dose and treatment duration). In addition, a significant decrease of the usage of HES solutions for infusion was noted in most EU Member States. This suggests that the previous communication measures although not sufficient to ensure full compliance, have had some effectiveness. It is therefore considered that a DHPC with more targeted messages and with the involvement of the learned societies in the distribution of this DHPC is likely to reinforce the effectiveness of this measure.

Besides, the CMDh acknowledged the PRAC's concern that non-adherence would not only be due to a lack of awareness by prescribers of the restrictions imposed to HES solutions for infusion. However, the CMDh considered that this assumption is not supported by sufficient evidence and might not be representative of a significant portion of the prescribers population and that in any case, the learned societies will have an important role in channelling the messages of the DHPC.

Therefore, the CMDh adopted a DHPC to inform HCPs of the results from the DUSs, the terms of the MA and the risks related to the use of HES solutions for infusion outside these terms, as well as the new additional risk minimisation measures. The CMDh also agreed on a communication plan for the dissemination of this DHPC.

As an overall conclusion, the CMDh considered that the risk minimisation described above would be feasible and effective and will have a synergistic effect as they allow targeting specific HCPs at all the steps of the prescription and administration of HES solutions for infusion.

4. Drug Utilisation Study (DUS)

In addition, the CMDh is of the view that the MAHs shall perform a Drug Utilisation Study, in order to assess the effectiveness of the new measures recommended. The conduct of this study will be a condition to the marketing authorisations for HES solutions for infusion.

The DUS protocol to be submitted by the MAHs should include clear objectives, focusing on prescribing decisions, especially adherence to indications and contraindications. Protocols should include a representative sample of EU Member States. They should also allow adequate description of national contexts to guarantee the adequate analysis and extrapolation of the outcome and justify potential

adjustments (i.e. successful/unsuccessful distribution of safety communications, adherence to the controlled access program, qualitative feedback from prescribers, etc). For this protocol, the MAH should take into account the experience gathered from the previously conducted DUS. The protocol should also include a measure of the primary outcomes at baseline. The primary outcomes should be common to all studied EU Member States.

The DUS protocol should be submitted for assessment to the PRAC within 3 months of the Commission Decision.

Progress on the ongoing DUS shall be reported within the upcoming PSUR. The DUS final study report shall be submitted within 24 months from the Commission Decision.

Grounds for differences with the PRAC recommendation

Whereas

- The CMDh took into consideration the revised PRAC recommendation as well as all the new elements submitted by the MAHs and the Member States regarding potential medical need and the feasibility and likely effectiveness of additional risk minimisation measures and available since the previous CMDh position adopted in January 2018.
- In particular, the CMDh noted the results of a consultation of Member States where the suspension of the marketing authorisation for HES solutions for infusion would have an impact on the clinical practice and concerns raised by those EU Member States about a potential medical need.
- The CMDh, through its representatives of Member States also considered feasibility at national level of some additional risk minimisation measures for which PRAC raised feasibility questions. In view of the insight that the CMDh has on the national healthcare systems, it agreed that the following additional risk minimisation measures are feasible and likely to be effective to minimise the risk of using HES solutions for infusion in contraindicated populations: the inclusion of an emphasised warning on the SmPC, PL, primary and secondary packaging, the circulation of a targeted DHPC and the implementation of a controlled access program.
- The CMDh also considered that the effectiveness of these additional risk minimisation measures must be assessed through the conduct of a drug utilisation study.

As a consequence, the CMDh is of the position that the benefit-risk balance of HES solutions for infusion remains favourable subject to the agreed amendments to the product information and the conditions to the marketing authorisation. The CMDh also concluded that the annual PSUR cycle should remain unchanged and would enable periodic review of the benefit-risk balance of these products and the impact of any data that would be generated.

Therefore the CMDh recommends the variation to the terms of the marketing authorisations for HES solutions for infusion.