Background information on the initiation of a referral under Article 107i of Directive 2001/83/EC on Hydroxyethyl starch (HES) by the Medical Products Agency

Disclaimer :

This assessment report was provided by the Swedish Competent Authority at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the Swedish Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the Swedish Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

An EU review under Article 107i of Directive 2001/83/EC for hydroxyethyl starch (HES)–containing solutions for infusion was finalised in December 2013 and concluded that these medicinal products are 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 – containing medicinal products do not outweigh the risks in these patient populations.

Therefore, the PRAC agreed that the therapeutic indication of HES containing medicinal products should be restricted to treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

The PRAC also agreed that additional measures needed to be implemented to minimise the risks. Thus, HES containing medicinal products should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. A maximum daily dose was implemented and the lowest possible effective dose should be employed. HES containing medicinal products were contraindicated in patients with renal impairment or renal replacement therapy but the contraindications were also extended to include other patient populations including patients with sepsis, critically ill patients and burns patients. The PRAC considered that the use of HES containing medicinal products must be discontinued at the first sign of renal injury. Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders.

The PRAC also imposed the conduct of randomised clinical trials to provide more evidence on the efficacy and safety, including the risk of 90-day mortality and renal failure. These studies in perioperative and trauma populations are underway.

Finally, the PRAC imposed to study drug utilization to verify adherence to the product information updated to include the above mentioned restrictions.

Results of two drug utilisation studies (DUS), undertaken in 11 EU Member states, have been submitted to the competent authorities with the aim to measure the level of adherence of the risk minimisation measures.

Results from these two studies show that the implemented restrictions in use have not been adhered to. Non-adherence to the revised product information was reported to range from 67% - 77%, including 20 – 34 % non-adherence to contraindications. On average, across all EU Member States included in the study, 9 % of patients exposed to HES solutions for infusion were critically ill, 5-8% of patients had renal impairment and 3-4 % of patients had sepsis. However, it should be noted that there was considerable variability in adherence, and thus in some EU Members States, these proportions were considerably higher.

The above raises serious concerns as use of HES containing medicinal products in patient populations which are contraindicated such as those who are critically ill, in patients with renal impairment, or with sepsis, is associated with a scientifically well-established risk for serious harm including mortality. Recent estimations of patient exposure across the EU indicate approximately 750 000 – 1.5 million patients exposed yearly.

In light of the scientifically well-established risk for serious harm including mortality when HES-containing medicinal products are used in contraindicated populations, together with these newly available data, Sweden seriously questions whether the benefit/risk balance of these medicinal products remains favourable. Consequently, in view of the serious public health impact, Sweden considers suspending the marketing authorisations for the HES containing medicinal products, and requests an urgent review of the matter at the European level.