LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 107i of Directive 2001/83/EC to the PRAC made by Sweden:

Product Name(s) in the Referring Member State, if applicable	**Voluven 60 mg/ml, DE/H/223/01** **Volulyte 60 mg/ml, DE/H/619/01** **Voluven 100 mg/ml, DE/H/1568/01** **Tetraspan 60 mg/ml, SE/H/609/01** **Tetraspan 100 mg/ml, SE/H/609/02** **Venofundin 60 mg/ml, SE/H/414/01** **Hesra, DE/H/1210/01** Hydroxyethyl starch (HES) containing medicinal products and related substances
Active substance(s)	Hydroxyethyl starch
Pharmaceutical form(s)	Solution for infusion
Strength(s)	All
Route(s) of Administration	Parenteral
Marketing Authorisation Holder(s) in the referring Member State	Fresenius Kabi AB B.Braun Melsungen AG Serumwerk Bernburg AG

Background

Hydroxyethyl starch (HES) solutions for infusion include products with starch with different molecular weights (mainly 130kD; 200kD) and substitution ratios (the number of hydroxyethyl groups per glucose molecule). HES solutions for infusion are authorised worldwide with the main indication for the treatment of hypovolaemia.

In 2012 and 2013, the Pharmacovigilance and Risk Assessment Committee (PRAC) reviewed the benefits and risks of HES-containing medicinal products 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.

In October 2013, the PRAC finalised its review as follows. The PRAC considered that the use of HES is associated with an increased risk of mortality and renal replacement therapy or

[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

renal impairment in patients with sepsis, critically ill and burn patients. Further, that the benefit of HES containing medicinal products outweighs the risk in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. The PRAC also concluded that HES containing medicinal products should be contraindicated in patients with sepsis, in critically ill and burn patients.

As conditions to the marketing authorisations, the PRAC requested that further studies be carried out on the use of these medicines in elective surgery and trauma patients, as well as to study drug utilisation to evaluate the effectiveness of the risk minimisation measures taken. Focus for the drug utilisation studies has been to evaluate the adherence to the restricted indications and new contraindications, which were implemented in the product information.

On 5th July 2017 and 9th October 2017, results from two drug utilisation studies on the effectiveness of the risk minimisation measures implemented have become available. These include utilisation data from in total 10 EU Member States. From these studies, it is evident that the implemented restrictions in use are not 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.

These data raise serious concerns as use of HES solutions for infusion 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[3, 4, 5]. Recent estimations of patient exposure across the EU indicate approximately 750 000 – 1.5 million patients exposed to HES solutions yearly.

In light of scientifically well-established risk for serious harm including mortality when HES solutions for infusion 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 above mentioned products, and requests an urgent review of the matter at the European level.

In view of the above, Sweden initiates an urgent union procedure under Article 107i of Directive 2001/83/EC and refers the matter to the PRAC which is requested to give its recommendation as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the position should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed [redacted] Date 2017-10-17

Marie Gårdmark
Direktör VO Tillstånd
Läkemedelsverket

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