



NATIONAL PBM BULLETIN

July 19, 2013

DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

HYDROXYETHYL STARCH SOLUTIONS ASSOCIATED WITH MORTALITY AND ACUTE KIDNEY INJURY

I. ISSUE

*FDA will require manufacturers to update the prescribing information for the entire class of hydroxyethyl starch (HES) products with a **BOXED WARNING** and additional cautions to the **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS** sections regarding an increased risk of:*

- *Mortality and renal injury requiring renal replacement therapy (RRT) in critically ill adult patients, including patients with sepsis and those admitted to the intensive care unit (ICU); and*
- *Excess bleeding, especially in patients undergoing open heart surgery in association with cardiopulmonary bypass.*

II. BACKGROUND

HES is a plasma volume substitute used for the treatment and prophylaxis of hypovolemia in adults and children. Researchers propose that adverse effects depend on the molecular weight of the HES formulations, with heavier starches having a greater persistence in the intravascular space as well as a greater risk of tissue accumulation. Studies have documented toxic effects on the kidney and an increase in mortality in patients receiving HES. However, findings have been inconsistent, and multiple trials from one investigator suspected to have engaged in scientific misconduct and data fabrication may have skewed the results of previous meta-analyses of studies of these products, making them appear safer and more efficacious than they are.

III. DISCUSSION

- FDA has reviewed clinical trials that show:
 - Greater incidence of renal damage and mortality in patients receiving HES.
 - One trial in ICU patients with severe sepsis (N=804) demonstrated greater mortality (relative risk, 1.17; 95% confidence interval [CI], 1.01-1.36; p=0.03) and RRT (relative risk, 1.35; 95% CI, 1.01-1.80; p=0.04) in the HES treatment arm compared with Ringer's acetate.
 - Another trial in adult patients admitted to the ICU for fluid resuscitation (N=7000) showed no difference in mortality (relative risk, 1.06; 95% CI, 0.96 -1.18; p=0.26 but increased RRT (relative risk, 1.21; 95% CI, 1.00-1.45; p=0.04) in patients receiving HES compared to those administered normal saline.
 - Additionally, a trial in severe sepsis patients indicated no difference in mortality (relative risk, 1.20; 95% CI, 0.83-1.74; p=0.33) and a trend for RRT (relative risk, 1.83; 95% CI, 0.93-3.59; p=0.06) in HES patients compared to those receiving normal saline.
- Multiple meta-analyses of randomized controlled trials using different HES preparations for fluid resuscitation in critically ill adult patients support the findings of increased mortality and renal injury requiring RRT.
- Additionally, eighteen meta-analyses revealed excess bleeding in patients undergoing open heart surgery related to cardiopulmonary bypass associated with HES use.
- FDA considers the above findings to be class effects.
- Further details regarding data describing these adverse events and accompanying guidance is available from the:
 - VA National PBM on the VA Intranet at: [Hydroxyethyl Starch \(HES\) Solutions in Critically Ill or Septic Patients](#); and
 - FDA at: <http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm358271.htm> .
- A review of VA's BCMA data for HES solution use by VISN shows over an 80% decrease in utilization across the VA from 2009 until present. VA purchase data from the first quarter in FY 2009 until the second quarter of FY 2013 reflects the approximate 80% decrease in use.

IV. PROVIDER RECOMMENDATIONS

FDA recommends that health care practitioners:

- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.

- Avoid use in patients with pre-existing renal dysfunction.
- Discontinue use of HES at the first sign of renal injury.
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy.
- Providers should continue to report any adverse reactions with the use of hydroxyethyl starch (HES) products by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

1. FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. <http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm358271.htm>. (Accessed July 11, 2013).
2. *Hydroxyethyl Starches (HES) in Critically Ill or Septic Patients – Update*. Washington, DC: Pharmacy Benefits Management Services and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs. April 2013. [Hydroxyethyl Starch \(HES\) Solutions in Critically Ill or Septic Patients](#)
3. Important New FDA Safety Communication for Voluven® (6% Hydroxyethyl Starch 130/0.4 in 0.9% Sodium Chloride Injection). http://www.hospira.com/Images/DHP%20Letter%20Event%207320%20FA307-01%20Final2_32-91866_1.pdf . (Accessed July 11, 2013).
4. Zarychanski R, bou-Setta AM, Turgeon AF, et al. Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation. *JAMA* 2013; 309: 678-688.
5. Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride for injection) Product Information. December 2007. Hospira, Inc. Lake Forest, Illinois 60045.

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., **primary care providers, critical care providers, anesthesiology, and surgery, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).