Post-Approval Pediatric Adverse Event Review:

Voluven®

(6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)

Pediatric Advisory Committee
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FDA

Background Drug Information

Drug:	Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)
Formulation:	Intravenous solution
Therapeutic Type:	Plasma volume expanders
Sponsor:	Fresenius Kabi
U.S. Approval	12/27/2007 (U.S. launch in September 2008)

Background: Plasma Volume Expanders

Colloidal Plasma Volume Expanders

- Examples: hetastarches, dextrans, albumins, gelatins
- Generally indicated for treatment of acute hypovolemia associated with surgery, sepsis, or trauma
- Mechanism: correct hypovolemia, in part, by drawing fluid from the extravascular space into the intravascular space

Background: Hetastarch (HES)

- Licensed in U.S. since early 1980s
- Approved products
  - Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride)
  - Hespan (6% hetastarch 600/0.75 in 0.9% sodium chloride)
  - Hextend (6% hetastarch 670/0.75 in lactated electrolyte)
- Known adverse events (AEs) associated with HES:
  - Pruritus (more common with HES than other colloids)
  - Anaphylaxis/anaphylactoid reactions
  - Decrease in blood coagulation factors, such as decrease in vonWillebrand Factor and Factor VIII

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Sponsor:	Fresenius Kabi
U.S. Approval:	12/27/2007 (U.S. launch in September 2008) Approved outside U.S. since 1999 and currently registered in 74 countries

Background: Voluven

Differences between Voluven & other HES products

- Short half life
- Less decrease in coagulation factors
- Higher ceiling dose

Background: Voluven

Indication:

- Treatment and prophylaxis of hypovolemia
- Not a substitute for plasma, red blood cells, or coagulation factors

Dosage

- Dosage and rate of infusion depends on estimated blood loss and degree of hemodynamic instability
- Maximum adult dose: 50 mL per kg/day (3500 mL for a 70 Kg patient)

Pre-Approval Clinical Studies (Adults)

- Pivotal study in US: Adults (>18yo) undergoing elective orthopedic surgery
  - Voluven (N=51) vs. Hespan (N=49)
  - Overall, no significant differences in serious AEs noted between the two treatment arms
  - AEs occurring in approximately 1% of Voluven-treated patients in the clinical trial:
    - Wound hemorrhage, anemia, pruritus
    - Coagulation disorders: aPTT elevated, PT prolonged
  - No serious coagulopathy in the Voluven group (*vs.* 3 cases of serious coagulopathy in Hespan patients)
- Several supportive studies from Europe (N= appx. 1300 subjects)

Pre-Approval Clinical Studies (Pediatrics)

Pediatric Study

- Children < 2 years old undergoing elective abdominal, cranial, thoracic, or urologic surgery

Age (months)	Voluven 6% (N=41)	Human Albumin 5% (N=41)
0 ≤ 6	18	23
6 ≤ 12	14	13
12 ≤ 18	9	4
>18	0	1

Pre-Approval Clinical Studies (Pediatrics)

Pediatric Study (continued)

- Voluven (N=41) or 5% albumin (N=41)
- Safety Assessment
  - aPTT (at post-operative day 1): no difference between groups
  - Serious AE incidence: no difference between groups (3 Voluven vs 2 albumin subjects experienced ≥1 SAE)

Pediatric Use*

- Limited clinical data available on use in children
- Clinical trial data available to support use in children 0-2 years old
- Ages of 2-12 years: safety and efficacy not established; post-market study is on-going.
- Ages >12 years: safety supported by studies in adults

*Voluven Package Insert, Section 8.4 Pediatric Use

Post-Approval Pediatric Clinical Studies

- Randomized controlled trial in the age group of 2 to 12 years
- Efficacy and safety of Voluven versus 5% albumin during open-heart surgery
  - Expected completion 12/2010
  - Approximately 60 subjects will be enrolled

Selected Labeling: Adverse Events Section*

All reported adverse events (pre- and post-licensure)

- *Immune system disorders;* <0.1%
  - Anaphylactoid reactions or Hypersensitivity

- *Skin and subcutaneous tissue disorders;* <10%
  - Dose dependent
  - Pruritus with prolonged administration and/or high doses
  - Observed with other HES

*Voluven Package Insert, Section 6 Adverse Reactions

Selected Labeling: Adverse Events Section *

All reported adverse events, continued

- *Laboratory Investigations*; <10%
  - Dose dependent
  - Rise in serum amylase; can confound diagnosis of pancreatitis
  - Dilutional effects may cause decrease in levels of coagulation factors and hematocrit

*Voluven Package Insert, Section 6 Adverse Reactions

Drug Utilization

- **Worldwide Voluven Use (Feb 2004 – Apr 2009)**
  - 69.1 million units sold
  - 21.2 million patients treated (sponsor estimate)
  - Note: dose varies depending on hemodynamic status, duration of treatment, and extent of hypovolemia
- Data on use in pediatric populations not available
- Source: Fresenius Kabi, Voluven Periodic Safety Update Reports, report periods 2/2004 through 4/2008 and 5/2008 through 4/2009

Post-Market AE Experience

AEs reported outside U.S. (Feb 2004-Apr 2009)

- 231 AEs (all ages) reported to sponsor worldwide
  - 179 from 4 clinical trials (153 involved non-serious lab value changes)
  - 52 spontaneous reports (15 involved serious and unlabeled AEs)
- Reporting rate of AEs = 0.0011%
  - 0.00025% for spontaneous reports only
  - Based on estimate of 21.2 million treated patients
- **All AEs reported to date are from outside U.S**.

AE Reports Since Approval

12/27/2007 to 6/30/2009

Crude Counts	All Reports		Serious*		Death	
	Total	US only	Total	US only	Total	US only
Adults (> 17)	9	0	8	0	0	0
Pediatrics (0 to 16)	1	0	1	0	0	0
Age unknown	0	0	0	0	0	0
All ages	10	0	9	0	0	0

*Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

Source: Adverse Event Reporting System, FDA

Pediatric Serious AE Reports Since Approval
12/27/2007 to 6/30/2009

Pediatric AE: Anaphylactic reaction

15 y/o with hx spina bifida, multiple orthopedic surgeries

- Severe hypotension 2 hours after induction of anesthesia
- Re-challenged with cephalosporins- no issues.
- Re-challenged with Voluven (3 ml, 10 ml and 30 ml).
  - After 30 ml, generalized cutaneous reaction (urticaria, redness and pruritus) and bronchial obstruction
  - Treated with adrenergics and crystalloid infusions; sxs resolved after 1 hour.

Adult Serious AE Reports Since Approval
12/27/2007 to 6/30/2009

Anaphylactic/Anaphylactoid reactions (n=2)

- Anaphylactic reaction (1)
  - Age 56; hypotension, rash, bronchospasm
  - Resolved with discontinuing Voluven and treatment with adrenergics, steroids
- Anaphylactoid reaction (1)
  - Age 47
  - Resolved; no other details provided

Adult Serious AE Reports Since Approval
12/27/2007 to 6/30/2009

Cardiac Events (n=2)

- Tachyarrhythmia and atrial fibrillation
  - 72 y/o in ICU for infection, chronic renal insufficiency
  - Treated with plasmapheresis, Voluven, and Albumin
  - During 5th treatment, developed tachycardia and atrial fibrillation after 100 mL of Voluven
  - Resolved with Voluven withdrawal and Ca gluconate
- Asystole
  - 57 y/o with bradycardia treated with multiple cardiac meds and volume expansion with Voluven
  - Asystole occurred 15 min later during surgical procedure Recovered.

Other Adult AE Reports Since Approval
12/27/2007 to 6/30/2009

Other Serious AEs (1 report each)

- Toxic epidermal necrolysis
- Renal failure
- Respiratory failure/ fluid overload/ ARDS
- Vasoplegia syndrome

Non-serious AE (1 report)

- Angioedema
  - 72 y/o treated with Voluven for blood loss during urologic procedure
  - Angioneurotic edema of tongue, lips, and fingers once 200 mL infused

Summary: Voluven

- This completes the one year post-approval pediatric review of adverse event reporting
- The safety review did not reveal new safety concerns for Voluven
- Additional efficacy and safety data in the 2-12 year age group will be collected in the on-going post-market study.
- Anaphylactic reactions are a known risk with HES products and are included in the label (Warning and Precautions Section)
- FDA recommends continuing routine safety monitoring for Voluven
- Does the Advisory Committee concur?

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