

# NATIONAL PBM BULLETIN

April 28, 2015

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

## FERUMOXYTOL (FERAHEME): FDA RECOMMENDS STRONGER WARNINGS AND CHANGES TO PRESCRIBING INFORMATION TO DECREASE THE RISK FOR SERIOUS ALLERGIC REACTIONS

### I. ISSUE

The U.S. Food and Drug Administration (FDA) announced that it has strengthened the warning for serious, potentially fatal allergic reactions with ferumoxytol to a Boxed Warning. In addition, changes were made to the prescribing information as a result of reports of serious reactions, including death, that have occurred despite appropriate intervention.<sup>1</sup>

### II. BACKGROUND

Ferumoxytol is an intravenous (IV) iron replacement product approved for use in patients with chronic kidney disease (CKD) and iron deficiency anemia. As with all IV iron products, there is a risk for potentially life-threatening allergic reactions, with administration to be conducted only when emergency medical personnel and equipment are available to provide treatment if a serious allergic reaction were to occur.<sup>1,2</sup>

### III. DISCUSSION

In clinical trials, the rate of serious hypersensitivity with ferumoxytol was reported in 0.2% of patients (3/1,726). Adverse reactions including pruritus, rash, urticaria or wheezing, which could potentially be associated with a hypersensitivity reaction, were reported in 3.7% of these patients. Moderate to severe hypersensitivity reactions were reported in 2.6% (16/1,014) of patients treated with ferumoxytol in trials that excluded patients with Stage 4 or 5 CKD.<sup>1,2</sup>

The FDA Adverse Event Reporting System includes 79 cases of anaphylactic reactions associated with ferumoxytol (during the timeframe since approval and up through the first half of 2014), in patients ranging from 19 to 96 years of age. Of these reports, 18 were fatal, despite immediate medical intervention and attempts at emergency resuscitation. It was reported that almost half of the anaphylactic reactions occurred with the first dose. Approximately 75% of the cases (60/79) reported that the reaction began during the infusion, or within 5 minutes after administration of the dose. Symptoms frequently included cardiac arrest, hypotension, dyspnea, nausea, vomiting, and flushing. In 43% (34/79) of the patients, there was a history of drug allergy, with 24% reporting multiple drug allergies.<sup>1</sup>

An analysis of spontaneous reports submitted to the FDA compared adverse events among the IV iron replacement products (October 2009 through June 2010; refer to table below) and found the odds ratio (OR) for adverse events (i.e., death, serious, other major, other) per million units sold were significantly higher with ferumoxytol compared to iron sucrose or sodium ferric gluconate. There was no significant difference in rates of adverse events with iron sucrose vs. sodium ferric gluconate, except for a higher rate of serious adverse events (OR 2.18, 95% CI 1.07 to 4.41; p=0.038) with sodium ferric gluconate. The author noted that the increased rate of adverse events with ferumoxytol may have been due to this being the most recently approved IV iron at the time, where reporting of adverse events may have been increased in comparison to other agents that have been available for a longer period of time.<sup>3</sup>

#### IV Iron Adverse Drug Event (ADE) Comparison<sup>3</sup>

# Reports (*)	Iron sucrose	Sodium Ferric Gluconate	LMW Iron Dextran	HMW Iron Dextran	Ferumoxytol
Death	1 (0.11; 0.11)	1(0.33; 0.52)	5 (4.50; 4.50)	2 (6.04; 6.45)	6 (50; 10)
Serious ADE	21 (2.25; 2.24)	15 (4.92; 7.85)	3 (2.70; 2.70)	6 (18.13; 19.35)	70 (583.3; 116.67)
Other Major ADE	17 (1.82; 1.82)	3 (0.98; 1.57)	1 (0.90; 0.90)	14 (42.30; 45.16)	10 (83.3; 16.67)
Other ADE	10 (1.07; 1.07)	2 (0.66; 1.05)	1 (0.90; 0.90)	0 (0; 0)	2 (16.67; 3.33)

\* (Rates per million units sold; rates per million 100 mg equivalents)

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## IV. RECOMMENDATIONS

The manufacturer's product information includes the following Boxed Warning and recommendations:<sup>1,2</sup>

### WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS

*Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving ferumoxytol. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiopulmonary arrest.*

- *Only administer ferumoxytol when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions* [See Warnings and Precautions in prescribing information]
- *Observe for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following ferumoxytol infusion including monitoring of blood pressure and pulse during and after ferumoxytol administration* [See Warnings and Precautions in prescribing information]
- *Hypersensitivity reactions have occurred in patients in whom a previous ferumoxytol dose was tolerated* [See Warnings and Precautions in prescribing information]

In addition, FDA makes the following recommendations:<sup>1</sup>

- *Only administer IV iron products to patients who require IV iron therapy.*
- *Do not administer ferumoxytol to patients with a history of allergic reaction to ferumoxytol or other IV iron products.*
- *Only administer diluted ferumoxytol as an IV infusion over a minimum of 15 minutes. Ferumoxytol should not be given as an undiluted IV injection.*
- *Closely monitor patients for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during ferumoxytol administration for at least 30 minutes following each infusion.*
- *Carefully consider the potential risks and benefits of ferumoxytol administration in elderly patients with multiple or serious medical conditions, as these patients may experience more severe reactions.*
- *Carefully consider the potential risks and benefits of ferumoxytol administration in patients with a history of multiple drug allergies. Patients with multiple drug allergies may also be at higher risk.*

Of the available IV iron products, iron sucrose, sodium ferric gluconate, and low-molecular weight iron dextran are listed on the VA National Formulary. Ferumoxytol and ferric carboxymaltose may be requested for select patients via the non-formulary process at local facilities (refer to [PBM Drug Monographs](#); [Clinical Recommendations, Iron \(Intravenous\) in CKD](#)).

Providers should continue to report any adverse reactions with the use of ferumoxytol, or any IV iron replacement product, 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 Drug Safety Communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug FeraHEME (ferumoxytol). <http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm>. (Accessed 04/01/15)
2. FERAHEME (ferumoxytol) injection [prescribing information]. Waltham, MA: AMAG Pharmaceuticals, Inc. March 2015.
3. Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health-Syst Pharm* 2012;69:310-20.

## 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., nephrologists, hematologists, primary care providers, subject matter experts and clinic staff, 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).