HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Feraheme safely and effectively. See full prescribing information for Feraheme.

FERAHEME® (ferumoxytol) Injection
For Intravenous (IV) use
Initial U.S. Approval: 2009

RECENT MAJOR CHANGES
Boxed Warning 03/2015
Dosage and Administration (2) 03/2015
Warnings and Precautions, Serious Hypersensitivity Reactions (5.1) 03/2015

WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS
See full prescribing information for complete boxed warning.

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

- Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. (5.1)
- Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following Feraheme infusion including monitoring of blood pressure and pulse during and after Feraheme administration. (5.1)
- Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated. (5.1)

INDICATIONS AND USAGE
Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD). (1)

DOSAGE AND ADMINISTRATION
- The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later.
- Administer Feraheme as an intravenous infusion in 50-200 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes

DOSAGE FORMS AND STRENGTHS
Injection: 510 mg iron per 17 mL (30 mg per mL) in single use vials. (3)

CONTRAINDICATIONS
- Known hypersensitivity to Feraheme or any of its components.
- History of allergic reaction to any intravenous iron product

WARNINGS AND PRECAUTIONS
- Greater risk of anaphylaxis in patients with multiple drug allergies. (5.1).
- Hypotension: Feraheme may cause hypotension. Monitor for signs and symptoms of hypotension following each administration of Feraheme. (5.2)
- Iron Overload: Regularly monitor hematologic responses during Feraheme therapy. Do not administer Feraheme to patients with iron overload. (5.3)
- Magnetic Resonance Imaging: Feraheme can alter magnetic resonance imaging (MRI) studies. (5.4)

ADVERSE REACTIONS
The most common adverse reactions (≥ 2%) following the administration of Feraheme are diarrhea, nausea, dizziness, hypotension, constipation, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS with Feraheme, contact AMAG Pharmaceuticals, Inc. at 1-877-411-2510, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2015
Feraheme is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD).

The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer Feraheme as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes. Administer while the patient is in a reclined or semi-reclined position.

For patients receiving hemodialysis, administer Feraheme once the blood pressure is stable and the patient has completed at least one hour of hemodialysis. Monitor for signs and symptoms of hypotension following each Feraheme infusion.

Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Closely observe patients for signs and symptoms of hypersensitivity including monitoring of blood pressure and pulse during and after Feraheme administration for at least 30 minutes and until clinically stable following completion of each infusion.

In clinical studies predominantly in patients with CKD, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of these subjects. In other trials excluding patients with Stages 4 and 5 CKD, moderate to severe hypersensitivity reactions were reported in 2.6% (26/1014) of patients treated with Feraheme.

In the post-marketing experience, fatal and serious anaphylactic type reactions presenting with cardiac/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of Feraheme may have more severe outcomes.

Severe adverse reactions of clinically significant hypotension have been reported. In clinical studies, hypotension was reported in 1.9% (33/1,726) of subjects, including three patients with serious hypotensive reactions. Hypotension has also been reported in the post-marketing experience. Monitor patients for signs and symptoms of hypotension following each Feraheme administration.

Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of Feraheme may have more severe outcomes.

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Regularly monitor the hematologic response during parenteral iron therapy. Do not administer Feraheme to patients with iron overload.

In the 24 hours following administration of Feraheme, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in the Feraheme complex.

Administration of Feraheme may transiently affect the diagnostic ability of MR imaging. Alteration of MR imaging studies may persist for up to 3 months following administration of Feraheme.

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Table 1: Adverse Reactions to Feraheme Reported in ≥1% of Patients with CKD

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Feraheme 2 × 510 mg (n = 605)</th>
<th>Oral Iron (n = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>2.0%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>1.8%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Edema</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.5%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>1.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Cough</td>
<td>1.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>1.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Rash</td>
<td>1.0%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme-treated patients included hypotension, infusion site swelling, increased serum ferritin level, chest pain, diarrhea, dizziness, ecchymosis, pruritus, chronic renal failure, and urticaria.

Following completion of the controlled phase of the trials, 69 patients received two additional 510 mg intravenous injections of Feraheme (for a total cumulative dose of 2.04 g). Adverse reactions following this repeat Feraheme dosing were similar in character and frequency to those observed following the first two intravenous injections.

In a placebo-controlled, cross-over trial, 713 patients with CKD received a single 510 mg dose of Feraheme. Adverse reactions reported by these patients were similar in character and frequency to those observed in other clinical trials.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following serious adverse reactions have been reported from the post-marketing experience with Feraheme: fatal, life-threatening, and serious anaphylactic-type reactions, cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, unresponsiveness, loss of consciousness, tachycardia/rhythm abnormalities, angioedema, ischemic myocardial events, congestive heart failure, pulse absent, and cyanosis. These adverse reactions have usually occurred within 30 minutes after the administration of Feraheme. Reactions have occurred following the first dose or subsequent doses of Feraheme.

7 DRUG INTERACTIONS

Drug-drug interaction studies with Feraheme were not conducted. Feraheme may reduce the absorption of concomitantly administered oral iron preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of Feraheme in pregnant women. In animal studies, ferumoxytol caused fetal malformations and decreased fetal weights at maternally toxic doses of 6 times the estimated human daily dose. Use Feraheme during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of ferumoxytol during organogenesis, at doses of 31.6 mg Fe/kg/day in rats and 16.5 mg Fe/kg/day in rabbits, did not result in maternal or fetal effects. These doses are approximately 2 times the estimated human daily dose based on body surface area. In rats, administration of ferumoxytol during organogenesis at a maternally toxic dose of 100 mg Fe/kg/day, approximately 6 times the estimated human daily dose based on body surface area, caused a decrease in fetal weights. In rabbits, administration of ferumoxytol during organogenesis at a maternally toxic dose of 45 mg Fe/kg/day, approximately 6 times the estimated human daily dose based on body surface area, was associated with external and/or soft tissue fetal malformations and decreased fetal weights.

8.3 Nursing Mothers

It is not known whether Feraheme is present in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to avoid Feraheme, taking into account the importance of Feraheme to the mother and the known benefits of nursing.

8.4 Pediatric Use

The safety and effectiveness of Feraheme in pediatric patients (less than 18 years old) have not been established.

8.5 Geriatric Use

In controlled clinical trials, 330 patients ≥ 65 years of age were treated with Feraheme. No overall differences in safety and efficacy were observed between older and younger patients in these trials, but greater sensitivity of older individuals cannot be ruled out. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of Feraheme may have more severe outcomes. The potential risks and benefits of Feraheme administration should be carefully considered in these patients [see Dosage and Administration (2) Serious Hypersensitivity Reactions (5.1) and Clinical Studies (14)].

10 OVERDOSAGE

Limited data are available regarding overdosage of Feraheme in humans.

Excessive dosages of Feraheme may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Feraheme to patients with iron overload [Warnings and Precautions (5.3)].

11 DESCRIPTION

Feraheme, an iron replacement product, is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylther. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of Feraheme is Fe₃O₄·C₈H₁₇O₇·H₂O·3NaCl with an apparent molecular weight of 750 kDa.

Feraheme Injection is an aqueous colloidal product that is formulated with mannitol. It is a black to reddish brown liquid, and is provided in single use vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of Feraheme Injection contains 30 mg of elemental iron and 44 mg of mannitol, and has low blemycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Feraheme consists of a superparamagnetic iron oxide that is coated with a carbohydrate shell, which helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received a supertherapeutic regimen of Feraheme (1.02 g given as two 510 mg doses within 24 hours), placebo or a single dose of 400 mg moxifloxacin (positive control). Results demonstrated no effect of Feraheme on QT interval durations. No clinically meaningful effect of Feraheme on heart rate was observed.
12.3 Pharmacokinetics

The pharmacokinetic (PK) behavior of Feraheme has been examined in healthy subjects and in patients with CKD stage 5D on hemodialysis. Feraheme exhibited dose-dependent, capacity-limited elimination from plasma with a half life of approximately 15 hours in humans. The clearance (CL) was decreased by increasing the dose of Feraheme. Volume of distribution (Vd) was consistent with plasma volume, and the mean maximum observed plasma concentration (Cmax) and terminal half-life (t1/2) values increased with dose. The estimated values of CL and Vd following two 510 mg doses of Feraheme administered intravenously within 24 hours were 69.1 mL/hr and 3.16 L, respectively. The Cmax and time of maximum concentration (tmax) were 206 mcg/mL and 0.32 hr, respectively. Rate of infusion had no influence on Feraheme PK parameters. No gender differences in Feraheme PK parameters were observed. Feraheme is not removed by hemodialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ferumoxytol was not tested for carcinogenic effects. In standard genotoxicity tests, ferumoxytol showed no evidence of mutagenic activity in an in vitro Ames test or clastogenic activity in either an in vitro chromosomal aberration assay or an in vivo micronucleus assay.

No adverse effects on fertility or general reproductive performance were noted in animal studies. Ferumoxytol had no effect on male or female fertility or general reproductive function in rats.

14 CLINICAL STUDIES

The safety and efficacy of Feraheme for the episodic treatment of iron deficiency anemia in patients with CKD were assessed in three randomized, open-label, controlled clinical trials (Trial 1, 2, and 3). These trials also included an uncontrolled, follow-up phase in which patients with persistent iron deficiency anemia could receive two additional 510 mg intravenous injections of Feraheme. The major efficacy results from the controlled phase of each study are shown in Table 2.

In all three trials, patients with CKD and iron deficiency anemia were randomized to treatment with Feraheme or oral iron. Feraheme was administered as two 510 mg intravenous single doses and oral iron (ferrous fumarate) was administered as a total daily dose of 200 mg elemental iron daily for 21 days. The major trial outcomes assessed the change in hemoglobin from baseline to Day 35.

Following completion of the controlled phase of each of the Phase 3 trials, patients who were iron deficient and anemic could receive two additional 510 mg intravenous injections of Feraheme. On Day 35 following these additional injections, the majority of these patients (70%) experienced an increase in hemoglobin and iron parameters (TSAT and ferritin). The mean change (±SD) in hemoglobin level from the retreatment baseline for patients with an increase in hemoglobin was 0.86 (± 0.68) g/dL, and was 0.5 (± 0.8) g/dL for all patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Feraheme is available in single use vials in the following package sizes (Table 3).

16.2 Stability and Storage

Store at 20° to 25°C (68° to 77°F). Excursions permitted to 15° – 30°C (59° – 86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

Refer patients to the FDA approved Patient Package Insert.

Prior to Feraheme administration:

- Question patients regarding a history of allergy to intravenous iron or any medications.
- Advise patients of the serious risks associated with Feraheme.
- Advise patients to immediately report any signs and symptoms of hypersensitivity that may develop during and following Feraheme administration, such as rash, itching, dizziness, lightheadedness, swelling, and breathing problems. Advise patients to seek immediate medical attention if these occur [see Warnings and Precautions (5)].