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
• Dosage and Administration (2) 06/2013

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 undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec), or as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for at least 15 minutes.
• The recommended Feraheme dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

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

CONTRAINDICATIONS
Known hypersensitivity to Feraheme or any of its components. (4)

WARNINGS AND PRECAUTIONS
• Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity during and after Feraheme administration for at least 30 minutes and until clinically stable following completion of each administration. (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.

Revised: 12/2013

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*Sections or subsections omitted from the full prescribing information are not listed.
5.1 Hypersensitivity Reactions

Feraheme injection may cause serious hypersensitivity reactions and hypotension [see Warnings and Precautions (5.1,5.2)].

In clinical studies, 7,726 subjects were exposed to Feraheme. 1,562 of these had CKD stages G1-3, 549 had CKD stage G4, and 517 had CKD stage G5. Subjects 46 and older were the most frequent in each group. Subjects included 75% male and 25% female. The mean age of the subjects was 63 years (range of 18 to 96 years).

During treatment with Feraheme, 0.8% of patients treated had serious hypersensitivity reactions and hypotension.

In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme-treated patients included hypotension, infusion site swelling, increased serum creatinine, hypotension, chest pain, dizziness, diaphoresis, pruritus, edemas, rashes, 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 these repeat Feraheme dosing were similar in character and frequency to those observed following the first two intravenous injections.

5.2 Hypotension

Severe adverse reactions of clinically significant hypotension have been reported. In clinical studies, hypotension was reported in 1.9% (3,517 of 185,218) of subjects. Including patients with serious hypotensive reactions. Hypotension has also been reported in the post-marketing experience [see Adverse Reactions in Post-Marketing Experience (8.1)].

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, although greater sensitivity of older individuals cannot be ruled out.

In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme-treated patients included hypotension, infusion site swelling, increased serum creatinine, hypotension, chest pain, dizziness, diaphoresis, urticaria, and hypotension. In clinical trials, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme-treated patients included hypotension, infusion site swelling, increased serum creatinine, hypotension, chest pain, dizziness, diaphoresis, pruritus, edemas, rashes, and urticaria.

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

2 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 intravenously, either as an undiluted slow intravenous injection or by infusion.

3 CONTRAINDICATIONS
Feraheme is contraindicated in patients with:
- Known hypersensitivity to Feraheme or any of its components

4 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have life-threatening potential and fatal outcomes, have been reported with Feraheme. In clinical trials, acute, anaphylactic, and anaphylactoid reactions were reported in 0.2% (3/1,726) of subjects receiving Feraheme. Observe patients for signs and symptoms of hypersensitivity and shock and for signs of anaphylactic reactions following each Feraheme injection.

5.2 Hypotension
Feraheme injection may cause serious hypersensitivity reactions and hypotension [see Warnings and Precautions (5.1, 5.2)]. In clinical trials, 1,726 subjects were exposed to Feraheme, 1,602 of which had CKD. Among these subjects, 45% were male and the median age was 63 years (range of 18 to 96 years). Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

6 ADVERSE REACTIONS
In clinical trials, adverse reactions leading to treatment discontinuation and occurring ≥2 Feraheme-treated patients included hypotension, infusion site swelling, increased serum creatinine, chest pain, diaphoresis, diarrhea, pruritus, and chronic renal failure, and urticaria.

7 INVESTIGATIONAL USE
Administer Feraheme to patients with iron overload [see Dosage and Administration (2)]. Do not administer Feraheme to patients with iron overload.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Feraheme is not a replacement product and is not a substitute for the iron-carboxymaltose complex with the iron-carboxymaltose complex within the macrophages. Iron then enters the intracellular storage pool (e.g., ferritin) or is transferred to plasma transferrin to transport to erythroid precursor cells for incorporation into hemoglobin.

9.2 Pharmacodynamics
Cardiac Electrophysiology
In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received a single intravenous Feraheme dose or placebo. Feraheme did not have a clinically significant effect on QT interval duration in these studies. No clinically significant changes in heart rate were observed.

10 OVERDOSE
No data are available regarding overdose of Feraheme in humans. Excessive dosages of Feraheme may result in accumulation of iron in the liver and portal areas, but the potential for iron overload is low. Do not administer Feraheme to patients with iron overload [see Warnings and Precautions (5.3)].

11 DESCRIPTION
Feraheme is an iron replacement product, is a non-chelatable magnetic (superparamagnetic iron oxide) coated with polyglycolic sorbitol carboxymethylxythym. The overall particle size is 17-21 nm in diameter. The chemical formula of Feraheme Injection, USP is Fe₃O₄·xH₂O. Each vial of Feraheme contains 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 a low hemoglobin-detected iron. The formation is isotonic with an osmolality of 270-330 mOsm/kg.

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 biocompatible iron from plasma components until the iron-carboxymaltose complex enters the reticuloendothelial system macrophages of the liver and bone marrow. Feraheme is released from the iron-carboxymaltose complex within the macrophages. Iron then enters the intracellular storage pool (e.g., ferritin) or is transferred to plasma transferrin to transport to erythroid precursor cells for incorporation into hemoglobin.
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. Trial 1 and 2 enrolled patients with non-dialysis dependent CKD and Trial 3 enrolled patients who were undergoing hemodialysis.

In Trial 1, the mean age of patients was 66 years (range, 23 to 95); 60% were female; 65% were Caucasian, 32% were Black, and 2% were other races. In the Feraheme and oral iron groups, 42% and 44% of patients, respectively, were receiving erythropoiesis stimulating agents (ESAs) at baseline.

In Trial 2, the mean age of patients was 65 years (range, 31 to 96); 61% were female; 58% were Caucasian, 35% were Black, and 7% were other races. In the Feraheme and oral iron groups, 36% and 43% of patients, respectively, were receiving ESAs at baseline.

In Trial 3, the mean age of patients was 60 years (range, 24 to 87); 43% were female; 54% were Caucasian, 59% were Black, and 7% were other races. All patients were receiving ESAs.

Table 2 shows the Baseline and mean change to Day 35 in hemoglobin (Hgb, g/dL), transferrin saturation (TSAT, %) and ferritin (ng/mL) in each treatment group for Trial 1, 2, and 3.

Table 2: Changes from Baseline to Day 35 in Hemoglobin, Transferrin Saturation and Ferritin (Intent to Treat Population)

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>Trial 1 Non-Dialysis CKD</th>
<th>Trial 2 Non-Dialysis CKD</th>
<th>Trial 3 CKD on Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Hgb</td>
<td>Feraheme n = 226</td>
<td>Oral Iron n = 77</td>
<td>Feraheme n = 228</td>
</tr>
<tr>
<td>(mean ± SD, g/dL)</td>
<td>9.9 ± 0.8</td>
<td>9.9 ± 0.7</td>
<td>10.0 ± 0.7</td>
</tr>
<tr>
<td>Hgb change from</td>
<td>Baseline at Day 35</td>
<td>Baseline at Day 35</td>
<td>Baseline at Day 35</td>
</tr>
<tr>
<td>(mean ± SD, g/dL)</td>
<td>1.2* ± 1.3</td>
<td>0.5 ± 1.0</td>
<td>0.8* ± 1.2</td>
</tr>
<tr>
<td>Baseline TSAT</td>
<td>(mean ± SD, %)</td>
<td>9.8 ± 5.4</td>
<td>10.4 ± 5.2</td>
</tr>
<tr>
<td>TSAT change from</td>
<td>Baseline at Day 35</td>
<td>Baseline at Day 35</td>
<td>Baseline at Day 35</td>
</tr>
<tr>
<td>(mean ± SD, %)</td>
<td>9.2 ± 9.4</td>
<td>0.3 ± 4.7</td>
<td>0.8 ± 9.2</td>
</tr>
<tr>
<td>Baseline ferritin</td>
<td>(mean ± SD, ng/mL)</td>
<td>123.7 ± 125.4</td>
<td>146.2 ± 136.3</td>
</tr>
<tr>
<td>Ferritin change</td>
<td>from Baseline at Day 35</td>
<td>300.7 ± 214.9</td>
<td>0.3 ± 82.0</td>
</tr>
<tr>
<td>(mean ± SD, ng/mL)</td>
<td>at Day 35 (mean ± SD, %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001 for main efficacy endpoint

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 for a total cumulative dose of 2.04 g. Overall, 69 patients received two additional 510 mg intravenous injections of Feraheme, and 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).

Table 3: Feraheme Packaging Description

<table>
<thead>
<tr>
<th>NDC Code</th>
<th>Dose / Total volume per vial</th>
<th>Vials / Carton</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC 59338-775-01</td>
<td>510 mg / 17 mL</td>
<td>1</td>
</tr>
<tr>
<td>NDC 59338-775-10</td>
<td>510 mg / 17 mL</td>
<td>10</td>
</tr>
</tbody>
</table>

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

Prior to Feraheme administration:
- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Feraheme.
- Advise patient to 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 [see Warnings and Precautions (5)].

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