FERAHEME® (ferumoxytol injection) Billing and Coding Information for Outpatient Services*

FERAHEME is indicated for the treatment of iron deficiency anemia (IDA) in adult patients:
• who have intolerance to oral iron or have had unsatisfactory response to oral iron or
• who have chronic kidney disease (CKD)

FERAHEME product and administration codes

<table>
<thead>
<tr>
<th>HCPCS¹</th>
<th>Injection, ferumoxytol, for treatment of IDA, 1 mg Q0138 non-ESRD use OR Q0139 ESRD on dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug administration CPT® codes²†</td>
<td>96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td>National Drug Codes (NDC)³²</td>
<td>59338-0775-01 FERAHEME 510 mg/17 mL, 1 vial 59338-0775-10 FERAHEME 510 mg/17 mL, 10 vials</td>
</tr>
</tbody>
</table>

*This table is provided for informational purposes only. Correct coding is the responsibility of the provider submitting the claim for the item or service. Please check with the payer to verify codes and specific billing requirements. AMAG Pharmaceuticals, Inc. does not make any representation or guarantees concerning reimbursement or coverage for any service or item.
¹CPT® is a registered trademark of the American Medical Association.
²Payer requirements regarding 10-digit and 11-digit NDC may vary.

Feraheme® (ferumoxytol injection) Important Safety Information

WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS
Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving Feraheme. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiorespiratory arrest.
• Only administer Feraheme as an intravenous infusion over at least 15 minutes and only when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.
• 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.
• Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

For questions regarding the billing and coding information above or for resources to support the claims appeal process, call: 844-635-AMAG (2624)
Website: Feraheme.com
Product, Administration, and Diagnosis Codes*

| HCPCS | Injection, ferumoxytol, for treatment of IDA, 1 mg
|       | Q0138 non-ESRD use OR Q0139 ESRD on dialysis

| Drug administration CPT® codes† | 96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

| National Drug Codes (NDC)‡ | 59338-0775-01 FERAHEME 510 mg/17 mL, 1 vial
|                           | 59338-0775-10 FERAHEME 510 mg/17 mL, 10 vials

| Diagnosis codes (ICD-10)§ | D50.0 Blood loss (chronic)
|                           | D50.1 Sideropenic dysphagia
|                           | D50.8 Poor iron absorption
|                           | D50.9 Iron deficiency anemia, unspecified

Confirm iron deficiency before using the following codes:

D63.0 Anemia in neoplastic disease
CODE NEOPLASM FIRST
D63.1 Anemia in chronic kidney disease
CODE CKD STAGE
D63.8 Anemia in other chronic diseases classified elsewhere
CODE UNDERLYING DISEASE FIRST
D64.81 Antineoplastic chemotherapy-induced anemia

Feraheme Important Safety Information (cont’d)

Contraindications
Feraheme is contraindicated in patients with known hypersensitivity to Feraheme or any of its components or a history of allergic reaction to any intravenous iron product.

Warnings and Precautions
Hypersensitivity: In addition to the fatal and serious adverse reactions in the Boxed Warning, other adverse reactions associated with hypersensitivity have occurred (pruritus, rash, urticaria, and wheezing). Allergic reactions have occurred following the first dose or subsequent doses in patients in whom a previous dose was tolerated. Patients with a history of multiple drug allergies may have a greater risk of anaphylaxis with parenteral iron products. Carefully consider the potential risks and benefits before administering Feraheme to these patients. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of Feraheme may have more severe outcomes.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.
# Codes Pertaining to IDA Underlying Conditions*

<table>
<thead>
<tr>
<th>Diagnosis codes (ICD-10)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>E83.10 Iron metabolism</td>
</tr>
<tr>
<td>E83.19 Other disorders of iron metabolism, specified NEC</td>
</tr>
<tr>
<td>K50.00, K50.90, K50.919 Crohn’s disease (regional enteritis)</td>
</tr>
<tr>
<td>K51.00, K51.90, K51.919 Pancolitis, ulcerative colitis, complication</td>
</tr>
<tr>
<td>K90.0 Celiac disease</td>
</tr>
<tr>
<td>K90.49 Malabsorption due to intolerance</td>
</tr>
<tr>
<td>K90.89 Intestinal malabsorption, specified NEC</td>
</tr>
<tr>
<td>K90.9 Intestinal malabsorption</td>
</tr>
<tr>
<td>N18.1 CKD, stage 1</td>
</tr>
<tr>
<td>N18.2 CKD, stage 2</td>
</tr>
<tr>
<td>N18.3 CKD, stage 3</td>
</tr>
<tr>
<td>N18.4 CKD, stage 4</td>
</tr>
<tr>
<td>N18.5 CKD, stage 5</td>
</tr>
<tr>
<td>N18.6 CKD, end-stage (failure)</td>
</tr>
<tr>
<td>N18.9 CKD</td>
</tr>
<tr>
<td>N92.0, N92.6 Excessive, frequent, and irregular menstruation</td>
</tr>
<tr>
<td>N95.0 Postmenopausal bleeding</td>
</tr>
<tr>
<td>T45.4X5 [A,S,D] Adverse effect of iron and its compounds</td>
</tr>
<tr>
<td>T50.905 [A,S,D] Adverse effect of unspecified drugs, medicaments, and biological substances</td>
</tr>
</tbody>
</table>

*This table is provided for informational purposes only. Correct coding is the responsibility of the provider submitting the claim for the item or service. Please check with the payer to verify codes and specific billing requirements. AMAG Pharmaceuticals, Inc. does not make any representation or guarantees concerning reimbursement or coverage for any service or item.

†CPT® is a registered trademark of the American Medical Association.

‡Payer requirements regarding 10-digit and 11-digit NDC may vary.


Please see **Important Safety Information** throughout and accompanying full **Prescribing Information**, including **Boxed Warning**.
Warnings and Precautions (cont'd)

Hypotension: Feraheme may cause clinically significant hypotension. Monitor patients for signs and symptoms of hypotension following each Feraheme administration.

Iron Overload: 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.

Magnetic Resonance (MR) Imaging Test Interference: 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 the last Feraheme dose. Maximum alteration of vascular MR imaging is anticipated to be evident for 1 – 2 days following Feraheme administration.

Adverse Reactions
The most common adverse reactions (≥ 2%) are diarrhea, headache, nausea, dizziness, hypotension, constipation, and peripheral edema.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

Visit Feraheme.com for more information.

INDICATIONS AND USAGE
Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients:
• who have intolerance to oral iron or have had unsatisfactory response to oral iron (1) or
• who have 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. (2)
• 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. (2)

DOSE FORMS AND STRENGTHS
Injection: 510 mg iron per 17 mL (30 mg per mL) in single-dose vials. (3)

CONTRAINDICATIONS
• Known hypersensitivity to Feraheme or any of its components. (4)
• History of allergic reaction to any intravenous iron product. (4)

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 Test Interference: Feraheme can alter magnetic resonance imaging (MRI) studies. (5.4)

ADVERSE REACTIONS
The most common adverse reactions (≥ 2%) are diarrhea, headache, 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

FULL PRESCRIBING INFORMATION: CONTENTS*
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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/cardiorespiratory arrest.
• Only administer Feraheme as an intravenous infusion over at least 15 minutes and only 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)

Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients:
• who have intolerance to oral iron or have had unsatisfactory response to oral iron (1) or
• who have chronic kidney disease (CKD). (1)
WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS

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

- Only administer Feraheme as an intravenous infusion over at least 15 minutes and only when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions [see Warnings and Precautions (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 [see Warnings and Precautions (5.1)].
- Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

Feraheme is indicated for the treatment of iron deficiency anemia (IDA) in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron or
- who have 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 7 days later. Administer Feraheme as an intravenous infusion in 10-200 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. Feraheme does not contain antimicrobial preservatives. Discard unused portion. Feraheme, when added to intravenous infusion bags containing either 0.9% Sodium Chloride Injection, USP (normal saline), or 5% Dextrose Injection, USP, at concentrations of 2-8 mg elemental iron per mL, should be used immediately but may be stored at controlled room temperature (25°C ± 2°C) for up to 4 hours or refrigerated (2-8°C) for up to 48 hours.

The dosage is expressed in terms of mg of elemental iron, with each mL of Feraheme containing 30 mg of elemental iron. Evaluate the hematologic response (hemoglobin, ferritin, iron and transferrin saturation) at least one month following the second Feraheme infusion.

The recommended Feraheme dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

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.

Allow at least 30 minutes between administration of Feraheme and administration of other medications that could potentially cause serious hypersensitivity reactions and/or hypotension, such as chemotherapeutic agents or monoclonal antibodies.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Feraheme injection is available in single-dose vials. Each vial contains 510 mg of elemental iron in 17 mL (30 mg per mL).

4 CONTRAINDICATIONS

Feraheme is contraindicated in patients with:

- Known hypersensitivity to Feraheme or any of its components [see Warnings and Precautions (5.1)].
- History of allergic reaction to any intravenous iron product [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Hypersensitivity Reactions

Fetal and serious hypersensitivity reactions including anaphylaxis, presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, or unresponsiveness have occurred in patients receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity have occurred (pruritus, rash, urticaria, and wheezing). These reactions have occurred following the first dose or subsequent doses in patients in whom a previous Feraheme dose was tolerated.

Patients with a history of multiple drug allergies may have a greater risk of anaphylaxis with parenteral iron products. Carefully consider the potential risks and benefits before administering Feraheme to these patients.

Only administer Feraheme as an intravenous infusion over at least 15 minutes and only 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 [see Adverse Reactions (6.2)].

In a clinical study in patients with IDA, regardless of etiology, hypersensitivity reactions were reported in 0.4% (4/997) of subjects receiving Feraheme administered as intravenous infusion over at least 15 minutes. These included one patient with severe hypersensitivity reaction and three patients with moderate hypersensitivity reactions.

In clinical studies predominately in patients with IDA and CKD, serious hypersensitivity reactions were reported in 0.2% (2/1,806) of subjects receiving Feraheme (administered as a rapid intravenous injection – prior method of administration no longer approved). Other adverse reactions potentially associated with hypersensitivity (i.e., pruritus, rash, urticaria or wheezing) were reported in 3.5% (63/1,806) of these subjects.

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 [see Boxed Warning, Adverse Reactions (6.2) and Use in Specific Populations (8.3)].

5.2 Hypotension

Feraheme may cause clinically significant hypotension.

In a clinical study with Feraheme in patients with IDA, regardless of etiology, moderate hypotension was reported in 0.2% (2/997) of subjects receiving Feraheme administered as intravenous infusion over at least 15 minutes.

In clinical studies in patients with IDA and CKD, hypotension was reported in 1.9% (36/1,806) of subjects, including three patients with serious hypotensive reactions, who had received Feraheme as a rapid intravenous injection (prior method of administration no longer approved).

Hypotension has also been reported in the post-marketing experience [see Adverse Reactions (6.2)]. Monitor patients for signs and symptoms of hypotension following each Feraheme administration [see Dosage and Administration (2) and Warnings and Precautions (5.1)].

5.3 Iron Overload

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemochromatosis. Regularly monitor the hematologic response during parenteral iron therapy [see Dosage and Administration (2)]. 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.

5.4 Magnetic Resonance (MR) Imaging Test Interference

Administration of Feraheme may transiently affect the diagnostic ability of MR imaging. Conduct anticipated MR imaging studies prior to the administration of Feraheme.

Alteration of MR imaging studies may persist for up to 3 months following the last Feraheme dose. If MR imaging is required within 3 months after Feraheme administration, use T1- or proton density-weighted MR pulse sequences to minimize the Feraheme effects; MR imaging using T2-weighted pulse sequences should not be performed earlier than 4 weeks after the administration of Feraheme. Maximum alteration of vascular MR imaging is anticipated to be evident for 1 – 2 days following Feraheme administration [see Clinical Pharmacology (12.3)].

Feraheme will not interfere with X-ray, computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound or nuclear medicine imaging.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Serious Hypersensitivity Reactions [see Warnings and Precautions (5.1)]
- Hypotension [see Warnings and Precautions (5.2)]
- Iron Overload [see Warnings and Precautions (5.3)]
- Magnetic Resonance (MR) Imaging Test Interference [see Warnings and Precautions (5.4)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies, 3,968 subjects were exposed to Feraheme. Of these subjects 31% were male and the median age was 54 years (range of 18 to 96 years).

The data described below reflect exposure to Feraheme in 997 patients exposed to a 1.02 g course of ferumoxytrol administered as two 510 mg intravenous (IV) doses: 992 subjects (99.5%) received at least 1 complete dose of ferumoxytrol and 846 subjects (85.9%) received 2 complete doses. The mean cumulative IV iron exposure was 993.80 ± 119.085 mg.

The safety of Feraheme was studied in a randomized, multicenter, double-blind clinical trial in patients with IDA (IDA Trial 3). [see Clinical Studies (7.4)]. In this trial, patients were randomized to two intravenous infusions of 510 mg (1.02 g) of Feraheme (n=497), or two intravenous infusions of 750 mg (1.500 g) of ferric carboxymaltose (FCM) (n=1000). Both

[no notes on this page]
intraocular iron infusions were infused over a period of at least 15 minutes. Most patients received their second infusion of Feraheme and FCM 7 (±1) days after Dose 1. The mean (SD) age of the study population (N: 157) was 52.1 (17.1) years. The majority of patients were female (76.1%), white (71.4%) and non-Hispanic (81.8%). The mean (SD) hemoglobin at baseline for all patients was 10.4 (1.5) g/dL.

Serious adverse events were reported in 3.6% (71/197) of ferumoxytol- and FCM- treated patients. The most common (≥2 subjects) serious AE reported in Feraheme–treated patients were syncope, gastrointestinal, seizure, pneumonia, hemorrhagic anemia, and acute kidney injury. In FCM–treated patients the most common (≥2 subjects) serious AEs were syncope, cardiac failure, congestive heart failure, anemia, and renal failure.

Adverse reactions related to Feraheme and reported by ≥ 1% of Feraheme–treated patients in IDA Trial 3 are listed in Table 1.

### Table 1: Adverse Reactions to Feraheme Reported in ≥1% of IDA Patients in IDA Trial 3

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Feraheme 2 x 510 mg (N = 987) %</th>
<th>Ferric Carboxymaltose 2 x 750 mg (N = 1000) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

In IDA Trial 3, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme–treated patients included arthralgia (0.3%), dyspepsia (0.3%), flushing (0.2%), chest discomfort (0.2%), chest pain (0.2%), nausea (0.2%), back pain (0.2%), dizziness (0.2%) and headache (0.2%).

Across two clinical trials in patients with IDA (IDA Trial 1 and 2), [see Clinical Studies (14.1)], patients were randomized to: two injections (rapid intraocular infusion) – prior method of administration no longer approved) of 510 mg of Feraheme (n=1411), placebo (n=2000), or five injections (infusions of 200 mg of iron sucrose (n=199). Most patients received their second Feraheme injection 8 to 8 days after the first injection. Adverse reactions related to Feraheme and reported by ≥ 1% of Feraheme–treated patients in these trials were similar to those seen in Trial 3.

In Trials 1 and 2, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme–treated patients included hyperkalemia (0.6%), hypertension (0.3%), and rash (0.2%).

In addition, a total of 634 subjects enrolled in and completed participation in a Phase 3 open label extension study. Of these, 337 subjects met IDA treatment criteria and received Feraheme. Adverse reactions following this repeat Feraheme dosing were generally similar in type and frequency to those observed after the first two intraocular infusions.

Across three randomized clinical trials in patients with IDA and CKD (CKD Trials 1, 2, and 3), [see Clinical Studies (14.3)], a total of 605 patients were exposed to two injections of 510 mg of Feraheme and a total of 280 patients were exposed to 200 mg/day of oral iron for 21 days. Most patients received their second Feraheme injection 8 to 8 days after the first injection.

Adverse reactions related to Feraheme and reported by ≥ 1% of Feraheme–treated patients in the CKD randomized clinical trials are listed in Table 2. Diarrhea (4%), constipation (2.1%) and hypertension (1%) have also been reported in Feraheme–treated patients.

### Table 2: Adverse Reactions to Feraheme Reported in ≥1% of Patients with IDA and CKD Trials 1, 2 and 3

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Feraheme 2 x 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</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</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>Phoneias</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>1</td>
<td>1.4</td>
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<tr>
<td>Dypsnea</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

In these clinical trials in patients with IDA and CKD, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme–treated patients included hypotension (0.4%), chest pain (0.3%), and dizziness (0.3%).

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

### 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/arrhythm 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 concurrently administered oral iron preparations.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Limited available data with ferumoxytol use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with untreated iron deficiency anemia (IDA) in pregnancy (see Clinical Considerations). In animal studies, administration of ferumoxytol to pregnant rabbits during organogenesis caused adverse developmental outcomes including fetal malformations and decreased fetal weights at maternally toxic doses of 6 times the estimated human daily dose.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Clinical Considerations**

Drug–associated maternal and/or embryofetal risk

Un-treated iron deficiency anemia (IDA) in pregnancy is associated with adverse maternal outcomes such as post-partum anaemia. Adverse pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

#### Data

**Animal Data**

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 soft tissue fetal malformations and decreased fetal weights.

#### 8.2 Lactation

**Risk Summary**

There are no data on the presence of ferumoxytol in human milk, the effects on the breastfed child, or the effects on milk production. Ferumoxytol has been detected in the milk of lactating rats. However, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Feraheme and any potential adverse effects on the breastfed child from Feraheme or from the underlying maternal condition.

#### 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, 833 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 hypertension 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), Warnings and Precautions (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)]. Feraheme is not removed by hemodialysis.

11 DESCRIPTION

Feraheme is an iron replacement product containing ferumoxytol for intravenous infusion. Ferumoxytol is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglycitol sorbitol carboxymethyl ether. The overall colloidal particle size is 17–31 nm in diameter. The chemical formula of Feraheme is Fe₂₅₀₋₂₅₁₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋˓ninety two hundred and thirty-three mg/m²/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 supratherapeutic regimen of Feraheme (1.02 g given as two 510 mg doses within 24 hours), placebo or a single dose of 400 mg mosfloxacin (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, 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.

Ferumoxytol had no effect on male or female fertility or general reproductive function in rats. In a pre and postnatal developmental study in rats, intravenous administration of ferumoxytol from gestation day 6 until lactation day 23 at doses up to 60 mg/kg/day (approximately 3 times the daily human dose based on body surface area comparisons assuming a 60-kg person) had no effect on maternal delivery or numbers of liveborn offspring. Male offspring (F1) of pregnant rats administered Feraheme at a dose of 60 mg/kg/day had delayed sexual maturation and decreased reproductive competence. Female offspring (F1) of pregnant rats (F0) administered Feraheme at a dose of 60 mg/kg/day had delayed sexual maturation and decreased reproductive competence. Doses of 30 mg/kg/day and 60 mg/kg/day are approximately 2 and 3 times the daily human dose based on body surface area comparisons assuming a 60-kg person, respectively.

14 CLINICAL STUDIES

14.1 Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Table 3 shows changes from baseline to Week 5 in hemoglobin and transferrin saturation in IDA Trial 1 and 2.

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>IDA Trial 1</th>
<th>IDA Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Hgb mean (SD), g/dL</td>
<td>Feraheme: 8.9 (0.9)</td>
<td>Placebo: 8.8 (0.9)</td>
</tr>
<tr>
<td>Proportion of patients with Hgb increase of ≥2.0 g/dL at any time from Baseline to Week 5, %</td>
<td>81.1</td>
<td>55</td>
</tr>
<tr>
<td>Treatment Difference (% SD)</td>
<td>26.0 (71.2, 80.0)</td>
<td>2.6 (3.8, 9.1)</td>
</tr>
<tr>
<td>Mean change in Hgb from Baseline to Week 5 mean (SD), g/dL</td>
<td>2.6 (1.5)</td>
<td>0.1 (0.9)</td>
</tr>
<tr>
<td>Proportion of patients with Hgb increase of ≥2.0 g/dL at any time from Baseline to Week 5, %</td>
<td>50.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Baseline TSAT mean (SD), %</td>
<td>7.0 (12.9)</td>
<td>5.4 (4.9)</td>
</tr>
<tr>
<td>Mean change in TSAT from Baseline to Week 5 mean (SD), %</td>
<td>11.4 (15.1)</td>
<td>0.4 (5.8)</td>
</tr>
</tbody>
</table>

*p<0.001 for main efficacy endpoint

In IDA Trial 1, fatigue-related symptoms and impacts were assessed using a patient reported outcome instrument, FACT-Fatigue (score range from 0 to 52 with higher scores indicating less fatigue). After 5 weeks, Feraheme-treated patients reported greater improvement from baseline in the fatigue score (+11.7 ± 11.73 points) than did patients in the placebo arm (+6.8 ± 9.51 points) with a treatment difference of 4.9 (95% CI: 3.08-6.71) points. The safety of Feraheme in IDA patients with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used was also assessed in another randomized, multicenter, double-blind safety clinical trial (IDA Trial 3). Patients were randomized in a 1:1 ratio to either two infusions of 510 mg (±0.02 g) of Feraheme (n=987) or two infusions of 750 mg (±1.50 g) of ferric carboxymaltose (FCM) (n=1000). Both IV iron were infused over a period of at least 15 minutes. Most patients received their second infusion of Feraheme or FCM +1 days after the first infusion. This study included patients with any etiology of IDA including CKD excluding dialysis-dependent CKD.

In IDA Trial 3, the mean age of patients was 55 years (range, 18 to 96); 76% were female; 71% were Caucasian, 24% were Black, 3% were Asian, and 2% were other races. The study met the primary endpoint to demonstrate non-inferiority to FCM with respect to the percentage of patients who experienced moderate-to-severe hypersensitivity reactions (including anaphylaxis) or moderate-to-severe hypotension (Feraheme: 0.6%; FCM: 0.7%; treatment difference: -0.1%; exact 95% confidence interval -0.91% to +0.709).
Table 4 shows the mean increase from baseline to week 5 in hemoglobin (Hgb) per treatment with Feraheme or oral iron. Feraheme was administered as two 510 mg intravenous injections 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.

In a randomized, controlled clinical trial of 162 IDA patients with CKD (92 Non-Dialysis and 70 on Dialysis), mean change in hemoglobin from Baseline to Week 5 was 0.71 ± 0.03 g/dL for Feraheme-treated patients and 0.61 ±0.07 g/dL for iron sucrose-treated patients.

**HOW SUPPLIED/STORAGE AND HANDLING**

16.1 How Supplied
Feraheme is available in single-dose vials in the following package sizes (Table 6).

Table 5: Changes from Baseline to Day 35 in Hemoglobin (Hgb), Transferrin Saturation and Ferritin (Intent to Treat Population) in CKD Trials 1, 2 and 3

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>CKD Trial 1 Non-Dialysis</th>
<th>CKD Trial 2 Non-Dialysis</th>
<th>CKD Trial 3 Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feraheme</td>
<td>Oral Iron</td>
<td>Feraheme</td>
<td>Oral Iron</td>
</tr>
<tr>
<td>N = 226</td>
<td>N = 77</td>
<td>N = 228</td>
<td>N = 76</td>
</tr>
<tr>
<td>Baseline Hgb 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 Baseline at Day 35 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 mean (SD), %</td>
<td>9.8 (5.4)</td>
<td>10.4 (5.2)</td>
<td>11.3 (6.1)</td>
</tr>
<tr>
<td>TSAT change from Baseline at Day 35 mean (SD), %</td>
<td>9.2 (8.4)</td>
<td>0.3 (4.7)</td>
<td>9.8 (9.2)</td>
</tr>
<tr>
<td>Baseline ferritin mean (SD), ng/mL</td>
<td>123.7 (125.4)</td>
<td>146.2 (136.3)</td>
<td>146.1 (173.6)</td>
</tr>
<tr>
<td>Ferritin change from Baseline at Day 35 mean (SD), ng/mL</td>
<td>300.7 (214.9)</td>
<td>0.3 (82.0)</td>
<td>381.7 (278.6)</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.

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**HOW SUPPLIED/STORAGE AND HANDLING**

16.1 How Supplied
Feraheme is available in single-dose vials in the following package sizes (Table 6).

Table 6: 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>

**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
Advisse the patient to read the FDA-approved patient labeling (Patient Information).

Prior History of Allergies to Parenteral Iron Products
Advisse the patient to report any prior history of allergies to parenteral iron products (see Warnings and Precautions [5.1]).

Hypersensitivity Reactions
Advisse patients to immediately report any symptoms of hypersensitivity that may develop during and following Feraheme administration, such as rash, itching, dizziness, light-headedness, swelling, and breathing problems (see Warnings and Precautions [5.1]).

U.S. patients: 6,599,488 B1; 7,553,479 B2; 7,871,597 B2; 8,501,158 B2; 8,591,864 B2; 8,926,947 B2
Distributed by: AMAG Pharmaceuticals, Inc. Waltham, MA 02451