Information to Support Healthcare Provider's Medical Judgment to Prescribe Feraheme® (ferumoxytol injection) for Purposes of Health Insurance Coverage

AMAG would like to support your efforts in standing behind your prescribing decision when you determine Feraheme is the right choice for your iron deficiency anemia patients. If you believe Feraheme is in the best interest of your patients, please express this view to payers who require step edits to access Feraheme therapy on behalf of your patients. Below is information, which may be considered when demonstrating medical necessity and/or appealing a denial of coverage for Feraheme. Please use your professional judgment regarding your specific patient case(s).

Supporting your decision to prescribe Feraheme with help from Feraheme Assist

- If you've prescribed Feraheme for a patient, consider submitting the Feraheme Enrollment Form and completed prior authorization form to Feraheme Assist so they can help you navigate the prescription approval process
- If appropriate for your patient, consider providing the following information in the prior authorization
  - Considerations for medical necessity
  - Any state-specific language to indicate you do not want to use an alternate IV iron therapy
- If the prior authorization is denied, Feraheme Assist can help you navigate the appeals process

Considerations to support your decision to prescribe Feraheme

- Many patients with iron deficiency anemia, such as cancer patients and those with chronic kidney disease, are immunocompromised and should limit visits to their healthcare provider or hospital[1]
- During the COVID-19 pandemic, limiting risk of exposure to the virus is important for all patients regardless of whether they are immunocompromised
- Feraheme provides flexibility:
  - **Administration:** Feraheme only requires 2 infusions limiting the number of visits compared to the covered products* and no pre-treatment or test dose is required[2*]
  - **Dosing:** Feraheme infusions can be dosed as early as 3 days apart, allowing for a complete course of therapy in a shorter amount of time[2*]
  - **Management of materials:** Feraheme can be mixed with saline or dextrose and can be diluted in a range of volumes from 50mL to 200mL[2]
- Feraheme has demonstrated efficacy†:
  - Increase in hemoglobin levels[2]
  - Patient-reported outcome data specific to improvement of fatigue-related symptoms[2,3]
  - Sustained response to therapy reducing the need for repeat doses[4]
- Compliance with IV iron treatment is important. Across six Phase 3 RCTs noted in the prescribing information, 94.2% to 97.2% of Feraheme-treated patients completed both doses of the study medication[5]

Need more clinical information about Feraheme? Connect with our Drug Information team

Phone: 877.411.2510 | Email: amag@druginfo.com | Monday – Friday, 9 am–5 pm ET

Have patient-specific coverage questions? Connect with Feraheme Assist

Phone: 844.635.2624 | Email: info@ferahemeassist.com | Monday – Friday, 8 am–8 pm ET

Please see below for Important Safety Information including Boxed Warning

FERAHEME® (ferumoxytol injection) 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)

The recommended dose of FERAHEME is an initial 510 mg dose followed by a second 510 mg dose as early as 3 days and up to 8 days later, each dose infused over at least 15 minutes while the patient is in a reclined or semi-reclined position.

Important Safety Information for FERAHEME

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.**

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 (pruritis, 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.

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 below the **full Prescribing Information** for FERAHEME (ferumoxytol injection).

*Covered products include: INFed® (iron dextran), Ferrlecit® (sodium ferric gluconate complex) and/or Venofer® (iron sucrose). Dosing regimens to achieve at least 1 gram vary by drug and are based on indication. Please see the individual drug prescribing information at www.dailymed.nlm.nih.gov.

†The safety and efficacy of FERAHEME® have been assessed in seven phase 3 clinical trials described in the Feraheme label (in which 3,968 subjects were exposed to Feraheme). Please see prescribing information for study details.

Fatigue-related symptoms and impacts were assessed in a double-blind placebo-controlled trial (IDA Trial 1) using a patient reported outcome instrument, FACIT-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.

A phase 3, open-label, extension study assessed the safety and efficacy of FERAHEME for the episodic treatment of IDA over 6 months. Patients who had completed the 5-week, double-blind, placebo-controlled study (IDA Trial1) were eligible to enroll in the extension study. The extension study included a 14-day screening period followed by 6 months of observation during which patients were evaluated for IDA monthly. Those with persistent or recurrent IDA (Hgb<11.0 g/dL and TSAT <20%) at any evaluation visit, received a course of FERAHEME (2x510 mg, 3-8 days apart). Overall, 61% of Feraheme-treated patients never required a second course of treatment during the 6-month extension study.

References: 1. Syed-Ahmed M, Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. Adv Chronic Kidney Dis. 2019;26(1):8-15. 2. FERAHEME® [prescribing information]. AMAG Pharmaceuticals, Inc; February 2018. 3. Vadhan-Raj S, Strauss W, Ford D, et al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. Am J Hematol. 2014;89(1):7-12. 4. Vadhan Raj, David C. Ford, Naomi V. Dahl, Kristine Bernard, Zhu Li, Lee F. Allen, and William E. Strauss. Am J Hematol. 2016;91(2): E3-E5. 5. Data on file, AMAG Pharmaceuticals.

PP-FRH-US-00303 07/2020
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Waltham, MA 02451

Know your state's *Dispense as Written* requirements to help ensure your patients receive the medication that has been prescribed

Help ensure your patients receive the medication you have prescribed:

Complete the DAW line on the prescription form per state laws

Discuss the importance of the medication you have prescribed with your patients

Stand firm in your decision to help ensure patients receive the medication you have prescribed when pharmacists ask about generic substitution

Use the chart on the next page to determine what language or special requirements are required in your state to protect your prescribing decision.

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Dispense As Written Requirements

Laws in each state vary, so knowing your state's *Dispense as Written* requirements is important to help ensure the dispensing pharmacy correctly fills the medication you and your patient have discussed. Use the chart below for guidance on how to complete the *"Dispense as Written/Do Not Substitute"* line when handwriting a prescription.

Dispense As Written Requirements By State

State	On Each Prescription
Alabama	The prescriber must sign the prescription signature line labeled "Dispense as Written".
Alaska	In the physician's handwriting, the words "Brand Medically Necessary", "Dispense as Written", "Do Not Substitute", or other similar wording must appear on the prescription.
Arizona	Clearly display on the prescription the words "DAW", "Dispense as Written", "Do Not Substitute", "Medically Necessary" or other wording indicative of substitution not permitted.
Arkansas	The prescriber must sign the prescription signature line labeled "Dispense as Written".
California	The prescriber should personally indicate, in his or her own handwriting, "Do not substitute" or words of similar meaning.
Colorado	The prescriber must sign or initial the prescription signature line labeled "Dispense as Written".
Connecticut	In the physician's handwriting, the words "Brand Medically Necessary" or "No Substitution" must appear on the prescription.
Delaware	In the physician's handwriting, the words "Brand Necessary" or "Brand Medically Necessary" must appear on the prescription.
Florida	In the physician's handwriting, the words "Medically Necessary" must appear on the prescription.
Georgia	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Hawaii	In the physician's handwriting, the words "Brand Medically Necessary" or other similar words or phrases must appear on the prescription.
Idaho	Physician should indicate by any means that the brand name drug must be dispensed.
Illinois	Physician must indicate "may not substitute" in his or her own handwriting.
Indiana	The prescriber must sign the prescription signature line labeled "Dispense as Written". For Medicaid/ Medicare patients: in the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Iowa	In the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
Kansas	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Kentucky	In the physician's handwriting, the words "Do Not Substitute" must appear on the prescription.

See next page for additional states.

1 AL Code § 34-23-8 (2019) 2 Alaska Stat § 12 AAC 52.510 (2019) 3 Ariz. Rev Stat § 32-1963.01 4 AR Code § 17-92-503 (2018) 5 Cal. Com Code § 4073 6 Colo. Rev Stat § 12-42.5-122 7 CT Gen Stat § 20-619 (2019) 8 Del. Code tit. 24, § 2549 9 FL Stat § 465.025 10 GA Code § 26-4-81 (2018) 11 HI Rev Stat § 328-92 (2019) 12 ID Code § 54-1768 (2019) 13 225 Ill. Comp Stat § 85/25 14 Ind. Code § 16-42-22-6 15 IA Code § 155A.32 (2019) 16 KS Stat § 65-1637 (2018) 17 KY Rev Stat § 217.822 (2019)

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Dispense As Written Requirements

Dispense As Written Requirements By State

State	On Each Prescription
Louisiana	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription. For prescriptions reimbursable by state Medicaid programs, the prescriber shall handwrite the words "Brand Necessary" or "Brand Medically Necessary" on the prescription.
Maine	In the physician's handwriting, the words "Dispense as Written", "DAW", "Brand", "Brand Necessary", or "Brand Medically Necessary" must appear on the prescription.
Maryland	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Massachusetts	In the physician's handwriting, the words "No Substitution" must appear on the prescription.
Michigan	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Minnesota	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Mississippi	Physician shall sign on the line marked "Dispense as Written".
Missouri	In the physician's handwriting, the words "Brand Medically Necessary", "Dispense as Written", "Do Not Substitute", "DAW", or words of similar meaning must appear on the prescription.
Montana	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Nebraska	In the physician's handwriting, the words "Dispense as Written", "DAW", "Brand Medically Necessary", "BMN", "No Drug Product Selection", "NDPS", "No Generic Substitution" or similar statements must appear on the prescription.
Nevada	In the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
New Hampshire	In the physician's handwriting, the words "Medically Necessary" must appear on the prescription.
New Jersey	Physician must initial the DAW/Do Not Substitute line on the prescription.
New Mexico	In the physician's handwriting, the words "No Substitution" or "No Sub" must appear on the prescription.
New York	In the physician's handwriting, "DAW" must appear on the prescription.
North Carolina	The physician must sign the signature line labeled "Dispense as Written" OR in the physician's handwriting, the words "Dispense as Written" or words or abbreviations of the same meaning must appear on the prescription.
North Dakota	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Ohio	In the physician's handwriting, the words "Dispense as Written", "DAW", Do Not Substitute", "Brand Medically Necessary" or any other statement that indicates the intent to prevent substitution, must appear on the prescription.
Oklahoma	Pharmacist shall not substitute unless with the express permission of the prescriber.

See next page for additional states.

18 LA Admin Code § 46:2517 19 32 ME Rev Stat § 13781 (2019) 20 MD Health Occ Code § 12-504 (2018) 21 MA Gen L ch 112 § 12D (2019) 22 MI Comp L § 333.17755 (2019) 23 MN Stat § 151.21 (2019) 24 MS Code § 73-21-117 (2018) 25 MO Rev Stat § 338.056 (2019) 26 MT Code § 37-7-505 (2019) 27 Neb. Rev Stat § 38-28, 111 28 NV Rev Stat § 639.2583 (2019) 29 NH Rev Stat § 318:47-d (2019) 30 NJ Rev Stat 24 § 6E-7 31 NM Stat § 26-3-3 (2018) 32 NY U.C.C. Law § 6810 33 NC Gen Stat § 90-85.28 (2020) 34 ND Stat § 19-02.1-14.1 35 Ohio Rev Code § 4729.38 (2019) 36 OAC § 535:10-3-1.1 (2018)

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Dispense As Written Requirements

Dispense As Written Requirements By State

State	On Each Prescription
Oregon	In the physician's handwriting, the words "Do Not Substitute" must appear on the prescription.
Pennsylvania	In the physician's handwriting, the words "Brand Medically Necessary" or "Brand Necessary" must appear on the prescription.
Rhode Island	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
South Carolina	The physician must sign the prescription signature line labeled "Dispense as Written".
South Dakota	In the physician's handwriting, the words "Brand Necessary" or the equivalent must appear on the prescription.
Tennessee	In the physician's handwriting, the words "Brand Name Medically Necessary", "Dispense as Written", "Medically Necessary", "Brand Name", "No Generic" or any abbreviation of this language must appear on the prescription.
Texas	In the physician's handwriting, the words "Brand Necessary" or "Brand Medically Necessary" must appear on the prescription.
Utah	The physician must sign the prescription signature line labeled "Dispense as Written" OR in the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
Vermont	In the physician's handwriting, the words "Brand Necessary", "No substitution", "Dispense as Written" or "DAW" must appear on the prescription.
Virginia	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Washington	The physician must sign the prescription signature line labeled "Dispense as Written" OR handwrite the words "dispense as written", or words of similar meaning on the prescription.
Washington, D.C.	In the physician's handwriting, the words "Dispense as Written", or words of similar meaning, must appear on the prescription.
West Virginia	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Wisconsin	In the physician's handwriting, the words "No substitutions" or "N.S." must appear on the prescription.
Wyoming	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.

State regulations are subject to change. The above guidance is specific to handwritten prescriptions. If providing a prescription orally or electronically, and for the most current information regarding individual state requirements, always check with your state board of pharmacy.

Chart updated as of June 2020.

37 OR Rev Stat § 689.515 (2019) 38 Pa. Cons Stat § 18-25.53 39 RI Gen L § 5-19.1-19 (2019) 40 SC Code § 39-24-40 (2019) 41 SD Codified L § 36-11-46.2 (2019) 42 TN Code § 53-10-204 (2018) 43 TSPB § 309.3 44 UT Code § 58-17b-605 (2087) 45 18 V.S.A. § 4606 46 VA Code § 54.1-3408.03 (2019) 47 WA Rev Code § 69.41.120 (2018) 48 DC Code § 48-03.03 (2019) 49 WV Code § 30-5-12b (2019) 50 WI Stat § 450.13 (2019) 51 WY Stat § 33-24-148 (2019)

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NP-MKN-US-00230 06/20

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Feraheme®
ferumoxytol injection

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 use
Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

Boxed Warning	02/2018
Indication and Usage (1)	02/2018
Dosage and Administration (2)	12/2017
Warnings and Precautions, Serious Hypersensitivity Reactions (5.1)	02/2018

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)**

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)

DOSAGE 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

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING 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** [*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 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.

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

Fatal 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 predominantly in patients with IDA and CKD, serious hypersensitivity reactions were reported in 0.2% (4/1,806) of subjects receiving Feraheme (administered as a rapid intravenous injection – prior method of administration no longer approved). Other adverse reactions potentially associated with hypersensitivity (e.g., 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 (8.5)*].

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% (35/1,806) 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 hemosiderosis. 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 ferumoxytol administered as two 510 mg intravenous (IV) doses: 992 subjects (99.5%) received at least 1 complete dose of ferumoxytol and 946 subjects (94.9%) 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 (14.1)*]. In this trial, patients were randomized to two intravenous infusions of 510 mg (1.02 g) of Feraheme (n=997), or two intravenous infusions of 750 mg (1.500 g) of ferric carboxymaltose (FCM) (n=1000). Both

intravenous irons 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=1997) was 55.2 (17.16) 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% (71/1997) of ferumoxytol- and FCM- treated patients. The most common (≥2 subjects) serious AEs reported in Feraheme-treated patients were syncope, gastroenteritis, seizure, pneumonia, hemorrhagic anemia, and acute kidney injury. In FCM-treated patients the most common (≥2 subjects) serious AEs were syncope, cardiac failure congestive, angina pectoris, and atrial fibrillation.

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

Adverse Reactions	Feraheme 2 x 510 mg (N = 997) %	Ferric Carboxymaltose 2 x 750 mg (N = 1000) %
Headache	3.4	3.1
Nausea	1.8	3.4
Dizziness	1.5	1.6
Fatigue	1.5	1.2
Diarrhea	1	0.8
Back Pain	1	0.4

In IDA Trial 3, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 Feraheme-treated patients included arthralgia (0.3%), dyspnea (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 intravenous injection - prior method of administration no longer approved) of 510 mg of Feraheme (n=1,014), placebo (n=200), or five injections/infusions of 200 mg of iron sucrose (n=199). Most patients received their second Feraheme injection 3 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 hypersensitivity (0.6%), hypotension (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 intravenous injections.

Across three randomized clinical trials in patients with IDA and CKD (CKD Trials 1, 2, and 3), [*see Clinical Studies (14.2)*], 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 3 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

Adverse Reactions	Feraheme 2 x 510 mg (n = 605) %	Oral Iron (n = 280) %
Nausea	3.1	7.5
Dizziness	2.6	1.8
Hypotension	2.5	0.4
Peripheral Edema	2	3.2
Headache	1.8	2.1
Edema	1.5	1.4
Vomiting	1.5	5
Abdominal Pain	1.3	1.4
Chest Pain	1.3	0.7
Cough	1.3	1.4
Pruritus	1.2	0.4
Pyrexia	1	0.7
Back Pain	1	0
Muscle Spasms	1	1.4
Dyspnea	1	1.1
Rash	1	0.4

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 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.

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

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

Disease-associated maternal and/or embryo/fetal risk

Untreated iron deficiency anemia (IDA) in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. 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 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), 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 polyglucose sorbitol carboxymethylether. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of Feraheme is $Fe_{5874}O_{8752}$-$C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa.

Feraheme Injection is a sterile aqueous colloidal product that is formulated with mannitol. It is a black to reddish brown liquid, and is provided in single-dose vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of Feraheme Injection contains 30 mg of elemental iron, 30 mg polyglucose sorbitol carboxymethylether, and 44 mg of mannitol. 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 supratherapeutic 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 (C_{max}) and terminal half-life ($t_{1/2}$) 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 C_{max} and time of maximum concentration (t_{max}) 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. In a pre and postnatal development study in rats, intravenous administration of ferumoxytol from gestation day 6 until lactation day 20 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 (F0) administered ferumoxytol at a dose of 60 mg/kg/day had delayed sexual maturation and decreased reproductive competence. Female offspring (F1) of pregnant rats (F0) administered ferumoxytol at doses of 30 mg/kg/day or 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

IDA-301 Trial (referred to as IDA Trial 1) (NCT 01114139), IDA-302 Trial (referred to as IDA Trial 2) (NCT 01114204) and IDA-304 Trial (referred to as IDA Trial 3) (NCT 02694978)

The safety and efficacy of Feraheme in patients with iron deficiency anemia, regardless of etiology and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used, were assessed in two randomized, controlled clinical trials (IDA Trial 1 and 2) with Feraheme administered as a rapid intravenous injection (prior method of administration no longer approved). In IDA Trial 1, patients were randomized to treatment with Feraheme or placebo. In IDA Trial 2, patients were randomized to treatment with Feraheme or iron sucrose. Feraheme (510 mg) and placebo were administered as two intravenous single dose injections over 3-8 days, and iron sucrose (200 mg) was administered as 5 intravenous injections or infusions over a period of 14 days.

In IDA Trial 1, the mean age of patients was 45 years (range, 18 to 91); 89% were female; 56% were Caucasian, 25% were Black, 16% were Asian, and 3% were other races.

In IDA Trial 2, the mean age of patients was 48 years (range, 18 to 89); 83% were female; 84% were Caucasian, 11% were Asian, 1% were Black, and 4% were other races.

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

Table 3: Changes from Baseline to Week 5 in Hemoglobin (Hgb) and Transferrin Saturation in IDA Trial 1 and 2 (Intent to Treat Population)

	IDA Trial 1		IDA Trial 2	
ENDPOINT	Feraheme N = 608	Placebo N = 200	Feraheme N = 406	Iron Sucrose N = 199
Baseline Hgb mean (SD), g/dL	8.9 (0.9)	8.8 (0.9)	8.9 (0.9)	8.8 (1.0)
Proportion of patients with Hgb Increase of ≥2.0 g/dL at any time from Baseline to Week 5, %	81.1	5.5	84.0	81.4
Treatment Difference (%, 95% CI)	75.6* (71.2, 80.0)		2.6 (-3.9, 9.1)	
Mean change in Hgb from Baseline to Week 5 mean (SD), g/dL	2.6 (1.5)	0.1 (0.9)	2.9 (1.6)	2.7 (1.3)
Proportion of patients with Hgb ≥12 g/dL at any time from Baseline to Week 5, %	50.5	3.0	66.7	48.2
Baseline TSAT mean (SD) , %	7.0 (12.9)	5.4 (4.9)	6.1 (9.9)	5.5 (10.3)
Mean change in TSAT from Baseline to Week 5 mean (SD), %	11.4 (15.1)	0.4 (5.8)	15.7 (16.8)	11.9 (14.4)

* p≤0.001 for main efficacy endpoint

In IDA Trial 1, fatigue-related symptoms and impacts were assessed using a patient reported outcome instrument, FACIT-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 (1.020 g) of Feraheme (n=997) or two infusions of 750 mg (1.500 g) of ferric carboxymaltose (FCM) (n=1000). Both IV irons were infused over a period of at least 15 minutes. Most patients received their second infusion of Feraheme or FCM 7(+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 +0.70%).

Table 4 shows the mean increase from baseline to week 5 in hemoglobin (Hgb) per treatment (Feraheme 2 x 510 mg; FCM 2 x 750 mg) and per gram of iron administered (Feraheme 1.020 g; FCM 1.500 g) in IDA Trial 3.

Table 4: Summary of Hemoglobin (Hgb) Changes per Treatment and per Gram of Iron Administered From Baseline to Week 5 (Intent to Treat Population) in IDA Trial 3

ENDPOINT	Feraheme 2 x 510 mg (N = 997)	Ferric Carboxymaltose (FCM) 2 x 750 mg (N = 1000)
Baseline Hgb mean (SD); g/dL	10.42 (1.48)	10.39 (1.46)
Mean change in Hgb from Baseline to Week 5 per Gram of Iron Administered mean (SD); g/dL	1.35 (1.35)	1.10 (1.05)
Treatment Difference Per Gram of Iron[a] (%, 95% CI)	0.26 (0.17, 0.36)	
Mean change in Hgb from Baseline to Week 5 mean (SD); g/dL	1.38 (1.35)	1.63 (1.54)
Treatment Difference[a] (%, 95% CI)	-0.24 (-0.35, -0.13)	

[a] Adjusted for difference in baseline Hgb

In IDA Trial 3, the incidence of severe hypophosphatemia (defined by blood phosphorous of <0.6 mmol/L at week 2) in the patients receiving Feraheme (0.4% of patients) was less than those receiving FCM (38.7% of patients).

14.2 Iron Deficiency Anemia in Patients with Chronic Kidney Disease

Trial 62745-7 (referred to as CKD Trial 1) (NCT 00255437), Trial 62745-6 (referred to as CKD Trial 2) (NCT 00255424), and Trial 62745-5 (referred to as CKD Trial 3) (NCT 00233597)

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 (CKD Trial 1, 2 and 3) where Feraheme was administered as a rapid intravenous injection (prior method of administration - no longer approved). 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 5.

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 undiluted intravenous injections 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. CKD Trial 1 and 2 enrolled patients with non-dialysis dependent CKD and CKD Trial 3 enrolled patients who were undergoing hemodialysis.

In CKD 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 CKD 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 CKD Trial 3, the mean age of patients was 60 years (range, 24 to 87); 43% were female; 34% were Caucasian, 59% were Black, and 7% were other races. All patients were receiving ESAs.

Table 5 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 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

	CKD Trial 1 Non-Dialysis		CKD Trial 2) Non-Dialysis		CKD Trial 3 Dialysis	
ENDPOINT	Feraheme N = 226	Oral Iron N = 77	Feraheme N = 228	Oral Iron N = 76	Feraheme N = 114	Oral Iron N = 116
Baseline Hgb mean (SD), g/dL	9.9 (0.8)	9.9 (0.7)	10.0 (0.7)	10.0 (0.8)	10.6 (0.7)	10.7 (0.6)
Hgb change from Baseline at Day 35 mean (SD), g/dL	1.2* (1.3)	0.5 (1.0)	0.8* (1.2)	0.2 (1.0)	1.0* (1.1)	0.5 (1.1)
Baseline TSAT mean (SD), %	9.8 (5.4)	10.4 (5.2)	11.3 (6.1)	10.1 (5.5)	15.7 (7.2)	15.9 (6.3)
TSAT change from Baseline at Day 35 mean (SD), %	9.2 (9.4)	0.3 (4.7)	9.8 (9.2)	1.3 (6.4)	6.4 (12.6)	0.6 (8.3)
Baseline ferritin mean (SD), ng/mL	123.7 (125.4)	146.2 (136.3)	146.1 (173.6)	143.5 (144.9)	340.5 (159.1)	357.6 (171.7)
Ferritin change from Baseline at Day 35 mean (SD), ng/mL	300.7 (214.9)	0.3 (82.0)	381.7 (278.6)	6.9 (60.1)	233.9 (207.0)	-59.2 (106.2)

* $p \leq 0.001$ 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.

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 ±1.03 g/dL for Feraheme-treated patients and 0.61 ±0.97 g/dL for iron sucrose-treated patients.

16 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

NDC Code	Dose / Total volume per vial	Vials / Carton
NDC 59338-775-01	510 mg/ 17 mL	1
NDC 59338-775-10	510 mg/ 17 mL	10

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

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Prior History of Allergies to Parenteral Iron Products

Question patients regarding any prior history of allergies to parenteral iron products [*see Warnings and Precautions (5.1)*].

Hypersensitivity Reactions

Advise 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 Patents: 6,599,498 B1; 7,553,479 B2; 7,871,597 B2; 8,501,158 B2; 8,591,864 B2; 8,926,947 B2

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