# Understanding Iron Deficiency Anemia

*Feraheme® (ferumoxytol) Injection For Intravenous (IV) use is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD).*

Feraheme®
ferumoxytol
injection

## Introduction

If you or someone you know has iron deficiency anemia (IDA), this brochure may be for you. You'll find information about what it means to have IDA and how your doctor may treat it.

## What is anemia?

Anemia is a condition in which people do not have enough healthy red blood cells (RBCs). Without sufficient RBCs, the body doesn't have enough hemoglobin (Hgb). Hgb is the substance in RBCs that allows them to carry oxygen to the tissues of the body. When you aren't getting enough oxygen due to anemia or some other medical reason, you may start to feel tired, look pale, or have trouble breathing.

## How common is anemia?

Nearly 3.5 million Americans have some form of anemia. This number might be even greater since many people have anemia without knowing it.

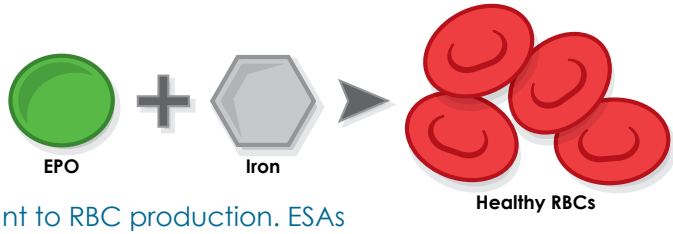
## What causes anemia?

There are many different causes of anemia, including:

- **Not enough iron**
- **Low levels of certain vitamins**
- **Blood disorders**
- **Issues with substances soaking up iron in your stomach**
- **Blood loss**
- **Not enough erythropoietin (EPO)**

## Building healthy RBCs

A doctor may prescribe an erythropoiesis stimulating agent (ESA) to help replace EPO in anemic patients.
EPO is a hormone that is important to RBC production. ESAs and iron supplements may be necessary to create healthy RBCs.




## What is IDA?

Anemia due to iron deficiency, or IDA, occurs when a person has too little iron in the body. IDA is the most common form of anemia.

### Common signs and symptoms of IDA

- **Pale skin**
- **Feeling tired**
- **Dizziness**
- **Shortness of breath**
- **Blue color to white part of the eyes**
- **Brittle fingernails**
- **Frequent headaches**

**Please see Important Safety Information About *Feraheme* on back cover.**

## How does my doctor know if I have IDA?

Several different blood tests help your doctor to determine whether you may have too little iron in your blood.

## Blood tests and what they measure

| Blood tests | What they measure |
|---|---|
| **Hgb** | **The level of a protein in red blood cells that carries oxygen throughout the body** |
| **Hematocrit** | **The percentage of blood that is made up of RBCs** |
| **Serum ferritin** | **The level of a protein in the cells that stores iron** |
| **Transferrin saturation (TSAT)** | **The amount of iron bound to transferrin, which carries iron from storage to sites where red blood cells are made** |

## Treating IDA

There are a number of ways to treat IDA, including taking iron pills or receiving intravenous (IV) injections. Due to certain medications, treatments, and/or conditions, your body may not absorb enough iron. Your doctor may determine that adding iron to your diet or taking pills doesn't work well enough. As a result, your doctor may suggest IV iron. Regarding intravenous iron:

- Various IV irons are available
- A healthcare professional injects an iron product into the bloodstream
- IV irons may cause side effects and allergic reactions, some of which can be life-threatening or fatal; please be sure to discuss these risks with your doctor

## What is *Feraheme*?

Feraheme® (ferumoxytol) Injection For Intravenous (IV) use is an intravenous iron approved for the treatment of adult iron deficiency anemia patients with chronic kidney disease (CKD). *Feraheme* provides a full dose of iron in 2 visits to your doctor.

In clinical studies, *Feraheme* was shown to raise patients' Hgb levels more effectively than oral iron. In certain people, such as those who have been diagnosed with CKD, anemia is especially common because inadequate kidney function can cause their red blood cell count to drop and anemia to develop.

*Feraheme* can only be administered by a doctor or nurse as an IV injection. *Feraheme* is not for people known to be allergic to *Feraheme* or any of its ingredients. Please see additional Important Safety Information.

**Please see full Prescribing Information in pocket.**

## What is CKD?

CKD occurs when the kidneys are unable to function properly. CKD usually develops slowly over time and has 5 stages. To determine your kidney function, your doctor will calculate your glomerular filtration rate (GFR) using the results of a blood test. After measuring GFR, your doctor will know how your kidneys are working.

## Stages of kidney disease

| Stage | Description | GFR[a] |
|---|---|---|
| 1 | Kidney damage for at least 3 months with normal GFR | 90 or above |
| 2 | Kidney damage for at least 3 months with mild decrease in GFR | 60 to 89 |
| 3 | Moderate decrease in GFR for at least 3 months | 30 to 59 |
| 4 | Severe reduction in GFR for at least 3 months | 15 to 29 |
| 5 | Kidney failure | Less than 15 |

[a]Your GFR number tells your doctor how much kidney function you have. As CKD progresses, your GFR number decreases.

## Who is at risk for CKD?

- People with diabetes
- People with high blood pressure (hypertension)
- People undergoing chemotherapy
- Older people

***Checking iron levels (such as serum ferritin and TSAT) regularly is important, as people with all stages of CKD are at risk for developing IDA.***

Feraheme®
ferumoxytol injection

# How does IV iron therapy with *Feraheme* help?

## How it's given


- *Feraheme* is an iron therapy that is given to adult patients with CKD through an IV injection
- A normal dose, one full gram of iron, is given in 2 doses
- After the first dose, the second dose is given within 3 to 8 days
- Each dose takes less than a minute to give. You will be watched for at least 30 minutes

## What to expect

- Intravenous iron therapy can help stimulate healthy RBC production in your body
- Adding iron to the body with *Feraheme* has been shown to significantly increase Hgb, the protein in RBCs that carries oxygen throughout the body
- Once you receive a full course of *Feraheme*, it can take several weeks for your iron levels to rise
- It is important to discuss treatment options and side effects with your healthcare provider. Your doctor will keep you in the office for at least 30 minutes after your injection in case you experience any allergic reactions or other side effects during or following your treatment

# Questions to ask your doctor

If you have CKD and are experiencing symptoms of IDA, or if you have been diagnosed with this condition, you should talk to your doctor about different iron treatments that are available, including IV iron.

## Consider the following questions:

**1.** When were my Hgb and iron levels last tested?

**2.** What are my Hgb and iron levels?

**3.** What can I do to help manage my anemia?

**4.** Is *Feraheme* right for me?

**5.** What are the possible side effects of *Feraheme*?

***Feraheme* is available only by prescription. *Feraheme* can cause side effects, some of which can be life-threatening or fatal. Call your doctor for medical advice about side effects. You are encouraged to report negative effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.**

**Please see full Prescribing Information in pocket.**

# Important Safety Information About *Feraheme*

*Feraheme* is an iron replacement product that has been approved to treat iron deficiency anemia (IDA) in adult patients with chronic kidney disease (CKD). *Feraheme* can only be administered by a doctor or nurse as an intravenous injection. *Feraheme* is not for people known to be allergic to *Feraheme* or any of its ingredients.

**You should be aware that treatment with *Feraheme* may cause life-threatening or fatal reactions.** These reactions were reported in clinical trials and in patients who received *Feraheme* after the clinical trials. **Serious reactions may include severe allergic reactions, cardiac arrest (sudden loss of heartbeat), a serious drop in blood pressure (hypotension), fainting, and unresponsiveness.** When tested in clinical trials, three out of 1,726 people who received *Feraheme* had a serious drop in blood pressure. Sixty-three additional people had other adverse reactions that may have been related to an allergic reaction. These included itching, rash, hives, and wheezing.

**After receiving *Feraheme*, you should be watched by a doctor or nurse for at least 30 minutes to make sure you do not have an allergic reaction or a drop in blood pressure.**

Receiving *Feraheme* may affect magnetic resonance imaging (MRI) for up to three months. Ultrasound, x-ray, and other imaging are not affected.

After receiving *Feraheme*, you may have diarrhea, nausea, dizziness, low blood pressure, constipation, and swelling of the arms and legs. If you develop any of these conditions, tell your doctor or nurse. You should also inform the FDA by calling 1-800-FDA-1088 or going online to the web site www.fda.gov/medwatch.

Some patients who received *Feraheme* after the clinical trials experienced serious side effects; however, it is not certain how often these side effects may occur or if they are definitely related to the use of *Feraheme*. Serious side effects included life-threatening allergic reactions, cardiac arrest (sudden loss of heartbeat), loss of breathing, serious drop in blood pressure, unresponsiveness, fainting or loss of consciousness, increased heart rate or other abnormal rhythms of the heart, swelling, loss of blood flow to the heart, heart failure, lack of a pulse (heartbeat), or blue coloration of the skin. These side effects happened in patients up to 30 minutes after receiving *Feraheme*.

**Please see full Prescribing Information in pocket.**

# Where to get more information

More information is available online. These websites provide trusted information to assist you in understanding and properly managing your condition.

- National Kidney Foundation (NKF) **www.kidney.org**
- American Association of Kidney Patients (AAKP) **www.aakp.org**
- National Kidney Disease Education Program (NKDEP) **www.nkdep.nih.gov**
- U.S. Food and Drug Administration **www.fda.gov**
- National Heart, Lung, and Blood Institute (NHLBI) **www.nhlbi.nih.gov**
- Centers for Disease Control and Prevention (CDC) **www.cdc.gov**
- American Academy of Family Physicians (AAFP) **www.aafp.org**



AMAG PHARMACEUTICALS

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 (IV) use**
**Initial U.S. Approval: 2009**

### RECENT MAJOR CHANGES

• Dosage and Administration (2) 06/2013

### INDICATIONS AND USAGE

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

### DOSAGE AND ADMINISTRATION

- The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later.
- Administer Feraheme as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec), or as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for at least 15 minutes.
- The recommended Feraheme dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity during and after Feraheme administration for at least 30 minutes and until clinically stable following completion of each administration. (5.1)
- Hypotension: Feraheme may cause hypotension. Monitor for signs and symptoms of hypotension following each administration of Feraheme. (5.2)
- Iron Overload: Regularly monitor hematologic responses during Feraheme therapy. Do not administer Feraheme to patients with iron overload. (5.3)
- Magnetic Resonance Imaging: Feraheme can alter magnetic resonance imaging (MRI) studies. (5.4)

### ADVERSE REACTIONS

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

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

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 12/2013**

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## FULL PRESCRIBING INFORMATION: CONTENTS*



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

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

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

## 2 DOSAGE AND ADMINISTRATION

The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer Feraheme intravenously, either as an undiluted slow intravenous injection or by infusion.

| Administration | Rate of delivery | Dilution |
|---|---|---|
| Undiluted intravenous injection | 1 mL/sec (30 mg/sec)<br>At least 17 seconds | No Dilution |
| Diluted intravenous infusion | At least 15 minutes | Dilute in 50 to 200 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. |

Feraheme, when added to intravenous infusion bags containing either 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.

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 injection. 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 injection.

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 use vials. Each vial contains 510 mg of elemental iron in 17 mL.

## 4 CONTRAINDICATIONS

Feraheme is contraindicated in patients with:

- Known hypersensitivity to Feraheme or any of its components

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

**Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Feraheme. Observe patients for signs and symptoms of hypersensitivity during and after Feraheme administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer the drug when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions** [*see Adverse Reactions (6.1)*]. **Anaphylactic type reactions presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported in the post-marketing experience** [*see Adverse Reactions from Post-marketing Spontaneous Reports (6.2)*]. In clinical studies, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of these subjects.

### 5.2 Hypotension

**Severe adverse reactions of clinically significant hypotension have been reported.** In clinical studies, hypotension was reported in 1.9% (33/1,726) of subjects, including three patients with serious hypotensive reactions. Hypotension has also been reported in the post-marketing experience [*see Adverse Reactions from Post-marketing Spontaneous Reports (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

Administration of Feraheme may transiently affect the diagnostic ability of MR imaging. Anticipated MR imaging studies should be conducted 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

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

In clinical studies, 1,726 subjects were exposed to Feraheme; 1,562 of these had CKD and 164 did not have CKD. Of these subjects 46% were male and the median age was 63 years (range of 18 to 96 years).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

### 6.1 Adverse Reactions in Clinical Studies

Across the three randomized clinical trials [Trial 1, 2, and 3, *see Clinical Studies (14)*], 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 randomized clinical trials are listed in Table 1. Diarrhea (4.0%), constipation (2.1%) and hypertension (1.0%) have also been reported in Feraheme-treated patients.

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

| Adverse Reactions | Feraheme 2 × 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 | 2.0% | 3.2% |
| Headache | 1.8% | 2.1% |
| Edema | 1.5% | 1.4% |
| Vomiting | 1.5% | 5.0% |
| 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% | 0.7% |
| Back Pain | 1.0% | 0% |
| Muscle Spasms | 1.0% | 1.4% |
| Dyspnea | 1.0% | 1.1% |
| Rash | 1.0% | 0.4% |

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

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

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

### 6.2 Adverse Reactions from Post-Marketing Spontaneous Reports

The following adverse reactions have been identified during post-approval use of Feraheme. Because these 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 spontaneous reports with Feraheme: life-threatening 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 occurred up to 30 minutes after the administration of Feraheme injection. Reactions have occurred following the first dose or subsequent doses of Feraheme.

## 7 DRUG INTERACTIONS

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

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

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety and effectiveness of Feraheme in pediatric patients have not been established.

### 8.5 Geriatric Use

In controlled clinical trials, 330 patients ≥ 65 years of age were treated with Feraheme. No overall differences in safety and efficacy were observed between older and younger patients in these trials, but greater sensitivity of older individuals cannot be ruled out. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [*see Dosage and Administration (2) and Clinical Studies (14)*].

## 10 OVERDOSAGE

No data are available regarding overdosage of Feraheme in humans. Excessive dosages of Feraheme may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Feraheme to patients with iron overload [*Warnings and Precautions (5.3)*].

## 11 DESCRIPTION

Feraheme, an iron replacement product, is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol 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 an aqueous colloidal product that is formulated with mannitol. It is a black to reddish brown liquid, and is provided in single use vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of Feraheme injection contains 30 mg of elemental iron and 44 mg of mannitol, and has low bleomycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received a 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.

## 14 CLINICAL STUDIES

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

In all three trials, patients with CKD and iron deficiency anemia were randomized to treatment with Feraheme or oral iron. Feraheme was administered as two 510 mg intravenous single doses and oral iron (ferrous fumarate) was administered as a total daily dose of 200 mg elemental iron daily for 21 days. The major trial outcomes assessed the change in hemoglobin from baseline to Day 35. Trial 1 and 2 enrolled patients with non-dialysis dependent CKD and Trial 3 enrolled patients who were undergoing hemodialysis.

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

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

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

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

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

| | **Trial 1 Non-Dialysis CKD** | | **Trial 2 Non-Dialysis CKD** | | **Trial 3 CKD on 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≤0.001 for main efficacy endpoint

Following completion of the controlled phase of each of the Phase 3 trials, patients who were iron deficient and anemic could receive two additional 510 mg intravenous injections of Feraheme for a total cumulative dose of 2.04 g. Overall, 69 patients received two additional 510 mg intravenous injections of Feraheme, and on Day 35 following these additional injections, the majority of these patients (70%) experienced an increase in hemoglobin and iron parameters (TSAT and ferritin). The mean change (±SD) in hemoglobin level from the retreatment baseline for patients with an increase in hemoglobin was 0.86 (± 0.68) g/dL and was 0.5 (± 0.8) g/dL for all patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

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

**Table 3: Feraheme Packaging Description**

| 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

Prior to Feraheme administration:

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Feraheme.
- Advise patient to report any signs and symptoms of hypersensitivity that may develop during and following Feraheme administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*].

US Patents: 6,599,498 B1; 7,553,479 B2; 7,871,597 B2; 8,501,158 B2

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