



Date: 10 Mar 2010

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To: Jessica Montealegre

Phone Number: (904) 380-4504

Fax Number: (904) 380-4504

From: AMAG Pharmaceuticals

Phone Number: (877) 411-2510

Dear Ms. Montealegre,

Thank you for your recent inquiry regarding Feraheme™ (ferumoxylol injection). In response to your inquiry, we have enclosed information on the following topic(s):

- Material Safety Data Sheet

We are pleased to supply the enclosed information as a professional courtesy. This information is not intended to promote any usage of Feraheme use that is not in accordance with the enclosed package insert.

If you have additional questions, please contact our Medical Information department at (877) 411-2510.

Sincerely,

Karen Bingham RN
Medical Specialist

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**MATERIAL SAFETY DATA SHEET**

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND COMPANY

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Canada)
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calls accepted)

Product Name or Substance Ferumoxytol Drug Substance

Synonyms	Polyglucose sorbitol carboxymethylether superparamagnetic iron oxide, Code 5128
Trade names	None identified
Chemical family	Iron preparation, semi-synthetic carbohydrate coated superparamagnetic iron oxide nanoparticle
Product use	Active pharmaceutical ingredient of ferumoxytol drug product
Note	The pharmacologic and toxicologic properties of this substance have not been fully characterized; this MSDS will be revisited as more data become available.
Issue Date	24 November 2009

SECTION 2 - HAZARDS IDENTIFICATION

Appearance	Black to reddish-brown aqueous liquid (in water)
Signal word	None required
Hazard Overview	Long-term inhalation exposure to high levels of iron oxide may cause effects on the respiratory system (pneumoconiosis, siderosis). It is unclear if similar effects would occur with inhalation exposure to ferumoxytol.
Known clinical effects	In clinical trials, patients treated intravenously with high doses of ferumoxytol experienced gastrointestinal effects, dizziness, hypotension and peripheral edema.
GHS signal word	None required
GHS classification	None required
GHS hazard symbol	None required
GHS hazard statements	None required
GHS precautionary statements	None required

SECTION 2 - HAZARDS IDENTIFICATION ...continued

EU indicator of danger None required

EU classification None required

Note This substance should be considered dangerous according to directive 1999/45/EC and Regulation EC No 1272/2008 (EU CLP). See Section 16 for full text of EU and GHS classifications. The GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ELIN</u> <u>CS#</u>	<u>Amount</u>	<u>EU</u> <u>Classification</u>	<u>GHS</u> <u>Classification</u>
Ferumoxytol	722492-56-0	N/A	~100%	Not Classified	Not Classified

Note The ingredient(s) listed above are considered hazardous. The remaining components are non-hazardous and/or present at amounts below reportable limits. See Section 16 for full text of EU and GHS classifications. The GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 4 - FIRST AID MEASURES

Immediate Medical Yes
Attention Needed

Eye Contact If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.

Skin Contact Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

Inhalation Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.

Ingestion If swallowed, call a physician immediately. Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.

Note to physician Medical conditions aggravated by exposure: None known or reported. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

Protection of first aid See Section 8 for Exposure Controls/Personal Protection recommendations.
responders

SECTION 5 - FIRE FIGHTING MEASURES

Flammability/Explosivity	Ferumoxytol has a negligible fire hazard when exposed to heat or flame. High concentrations of finely divided airborne particles can potentially explode if ignited.
Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Fire fighting instructions	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.
Hazardous combustion products	None.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated.
Spill cleanup methods	For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Wash spill area thoroughly with water. Collect spilled material, absorbent, and rinse water into suitable containers for proper disposal in accordance with applicable waste disposal regulations (see Section 13).
Environmental precautions	No information identified.

SECTION 7 - HANDLING AND STORAGE

General handling	Avoid contact with eyes, skin and other mucous membranes.
Storage conditions	Store at controlled room temperature (20- 25°C) away from incompatible materials. Excursions are permitted to 15-30°C. Ferumoxytol is stored in water.
Specific Use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	OEL values not submitted by AMAG are for iron oxide.
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SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

Exposure limit values

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Ferumoxytol	AMAG	TWA-8 HR	5 mg/m ³ (measured as Fe)
	ACGIH	TWA-8 HR	5 mg/m ³ (respirable fraction) (Iron oxide)
	Austria	TWA-8 HR	5 mg/m ³ (respirable fraction); 10 mg/m ³ (inhalable fraction) (Iron oxide)
	Austria	STEL	10 mg/m ³ (respirable fraction, 2 X 60 min) (Iron oxide)
	Belgium	TWA-8 HR	2 ppm (fume, as Fe); 5 mg/m ³ (fume, as Fe) (Iron oxide)
	Bulgaria, Finland	TWA-8 HR	5.0 mg/m ³ (as Fe) (Iron oxide)
	Denmark	TWA-8 HR	3.5 mg/m ³ (as Fe) (Iron oxide)
	Estonia, Sweden	TWA-8 HR	3.5 mg/m ³ (respirable dust, as Fe) (Iron oxide)
	France, Poland	TWA-8 HR	5 mg/m ³ (fume, as Fe) (Iron oxide)
	Germany	TWA-8 HR/STEL	1.5 mg/m ³ (respirable fraction)/10 mg/m ³ (as Fe) (Iron oxide)
	Greece	TWA-8 HR/STEL	10 mg/m ³ (as Fe) (Iron oxide)
	Hungary	TWA-8 HR	6 mg/m ³ (respirable dust) (Iron oxide)
	Ireland, United Kingdom	TWA-8 HR	5 mg/m ³ (fume, as Fe); 10 mg/m ³ (total inhalable dust, regulated under Rouge); 4 mg/m ³ (respirable dust, regulated under Rouge)
	Ireland	STEL	10 mg/m ³ (fume, as Fe) (Iron oxide)
	NIOSH	IDLH (Immediately dangerous to life or health)	2500 mg/m ³ (dust and fume, as Fe) (Iron oxide)
	NIOSH, Spain	TWA-8 HR	5 mg/m ³ (dust and fume, as Fe) (Iron oxide)

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

Exposure limit values

...continued

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
	Portugal	TWA-8 HR	5 mg/m ³ (respirable fraction, as Fe) (Iron oxide)
	Romania	TWA-8 HR/STEL	5/10 mg/m ³ (dust and fume) (Iron oxide)
	Slovak Republic	TWA-8 HR	1.5 mg/m ³ (Iron oxide)
	US OSHA	TWA-8 HR	10 mg/m ³ (fume) (Iron oxide)
	United Kingdom	STEL	10 mg/m ³ (fume, as Fe); 30 mg/m ³ (total inhalable, regulated under Rouge); 12 mg/m ³ (respirable, regulated under Rouge)
DNELs/PNECs	None identified.		
Exposure/Engineering controls	Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Use local exhaust and/or enclosure at dust-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling of powders. High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system.		
Respiratory protection	Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine tasks powder handling tasks, an approved and properly fitted air purifying respirator should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a powered air-purifying respirator equipped with HEPA filters or combination filters or a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where a lower level of respiratory protection may not provide adequate protection.		
Hand protection	Wear nitrile or other impervious gloves if skin contact is possible. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.		
Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.		

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

Eye protection	Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).
Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Physical form/Appearance	Black to reddish-brown aqueous liquid (in water)
Color	Black to reddish-brown
Odor	No information identified.
Odor threshold	No information identified.
pH	6-8 (in water)
Taste	No information identified.
Boiling point/boiling range	No information identified.
Melting point/melting range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	No information identified.
Explosive properties	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Oxidizing properties	No information identified.
Vapor pressure	No information identified
Molecular weight	~750 kDa
Molecular formula	$\text{Fe}_{5874}\text{O}_{8752} \cdot \text{C}_{11719}\text{H}_{18682}\text{O}_{9933}\text{Na}_{414}$

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

Density	No information identified.
Specific gravity	1.06 g/mL (in water)
Viscosity	2 CPS at 25°C (in water)
Water solubility	No information identified.
Solvent solubility	No information identified.
Autoflammability	No information identified.
Partition coefficient (<i>n-octanol/water</i>)	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Stable at controlled room temperature for at least 24 months.
Conditions to avoid	Avoid extreme temperatures.
Materials to avoid/Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.
Hazardous polymerization	Not expected to occur.

SECTION 11 - TOXICOLOGY INFORMATION

Route of entry	May be absorbed by inhalation, skin contact and ingestion.
Note	In non-clinical studies, doses of ferumoxylol were measured as Fe.

Acute toxicity

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Ferumoxylol	LD ₅₀	IV	Rat/Dog	>450 mg/kg (measured as Fe)
	LD ₅₀	Oral	Rat/Mouse	>15 g/kg (FeO _x)

SECTION 11 - TOXICOLOGY INFORMATION ...continued

Irritation/Corrosion	No localized edema or tissue irritation occurred after intravenous, perivenous, or intraarterial administration for formulated ferumoxytol.
Sensitization	Minimal potential for inducing anaphylactoid responses was observed in the rat paw edema model. Additionally, no potential was observed in a guinea pig study.
Repeat-dose toxicity	Repeat-dose toxicity studies with ferumoxytol at doses up to 12 mg(Fe)/kg/day for 13 weeks in rats and dogs demonstrated dose-dependent decreases in body weight gain and food consumption, and increases in pigmentation intensity. No systemic or immunological toxicity was observed at clinically relevant doses.
Reproductive toxicity	No adverse effects on fertility were observed in rats at intravenous doses as high as 18 mg (Fe)/kg/day ferumoxytol.
Developmental toxicity	Developmental toxicity was observed in rats and rabbits treated with ferumoxytol, but only at doses that were associated with maternal toxicity.
Genotoxicity	Negative in several genotoxicity studies.
Carcinogenicity	This substance is not listed by NTP, IARC, ACGIH or OSHA as a carcinogen.
Aspiration hazard	No data available.
Human health data	In clinical trials, patients treated intravenously with high doses of ferumoxytol experienced gastrointestinal effects, dizziness, hypotension and peripheral edema.

SECTION 12 - ECOLOGICAL INFORMATION

Aquatic Toxicity	No data available.
Persistence and Degradability	No data available.
Bioaccumulative potential	No data available.
Note	The environmental characteristics of the formulated product have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL INFORMATION

Disposal procedures	Used product should be disposed of according to local, state, and federal regulations. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.
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SECTION 14 - TRANSPORTATION INFORMATION

Transport This product is not regulated as a hazardous material/dangerous good under US DOT, Canada TDG, IATA, IMDG or EU ADR/RID.

SECTION 15 - REGULATORY INFORMATION

Compliance This MSDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines.

OSHA Hazardous Yes

EU label pictogram(s) None required

EU classification None required

Risk phrases None required

Safety phrases None required

WHMIS classification Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the MSDS contains all of the information required by those regulations.

WHMIS symbol(s) None required

GHS pictogram(s) None required

GHS signal word None required

GHS H and P phrases None required

TSCA status Drugs are exempt from TSCA.

SARA section 313 Not listed.

California proposition 65 Not listed.

SECTION 16 - OTHER

Full text of R phrases and EU Classifications Not available.

Full text of H phrases, P phrases and GHS classification Not available.

Recommended restrictions on use Do not take internally unless instructed by a physician.

Sources of data Information from published literature and internal company data.

SECTION 16 - OTHER ...continued

Abbreviations

ACGIH - American Conference of Government Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STEL - Short Term Exposure Limit; TDG - Transport Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System

Revisions

This is the first version of this MSDS.

Disclaimer

The above information is offered in good faith. It is based on data available to us which is believed to be correct and is intended only as a guide to the appropriate precautionary handling of the material by a properly trained person using this product. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions. **NO REPRESENTATION, WARRANTY, OR GUARANTEE, EXPRESS OR IMPLIED (INCLUDING A WARRANTY OF FITNESS OR MERCHANTABILITY FOR A PARTICULAR PURPOSE), IS MADE WITH RESPECT TO THE MATERIALS, THE COMPREHENSIVENESS OR ACCURACY OF THIS INFORMATION, THE RESULTS TO BE OBTAINED FROM THE USE THEREOF, OR THE HAZARDS CONNECTED WITH THE USE OF THE MATERIAL.** Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Material Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.

Feraheme™

ferumoxylol
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™ (ferumoxylol) Injection
For Intravenous (IV) use
Initial U.S. Approval: 2009

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 intravenous injection followed by a second 510 mg intravenous injection 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).
- The recommended Feraheme dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

DOSAGE FORMS AND STRENGTHS

Feraheme (30 mg/mL) is available for intravenous injection in single use vials. Each vial contains 510 mg of elemental iron in 17 mL.

CONTRAINDICATIONS

Evidence of iron overload. (4)

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

Anemia not caused by iron deficiency. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity for at least 30 minutes following the administration of Feraheme. (5.1)
- Hypotension: Feraheme may cause hypotension. Monitor for signs and symptoms of hypotension following the 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 ($\geq 2\%$) 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: 06/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Feraheme™ (ferumoxytol) Injection 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 intravenous injection followed by a second 510 mg intravenous injection 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). 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 (30 mg/mL) is available for intravenous injection in single use vials. Each vial contains 510 mg of elemental iron in 17 mL.

4 CONTRAINDICATIONS

Feraheme is contraindicated in patients with:

- Evidence of iron overload
- Known hypersensitivity to Feraheme or any of its components
- Anemia not caused by iron deficiency

5 WARNINGS AND PRECAUTIONS

5.1 HYPERSENSITIVITY REACTIONS

Feraheme may cause serious hypersensitivity reactions, including anaphylaxis and/or anaphylactoid reactions. 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. Observe patients for signs and symptoms of hypersensitivity for at least 30 minutes following Feraheme injection and only administer the drug when personnel and therapies are readily available for the treatment of hypersensitivity reactions [see *Adverse Reactions* (6.1)].

5.2 HYPOTENSION

Hypotension may follow Feraheme administration. In clinical studies, hypotension was reported in 1.9% (33/1,726) of subjects, including three patients with serious hypotensive reactions. Monitor patients for signs and symptoms of hypotension following 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 [see *Contraindications* (4)].

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 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	2.0%	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.

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, Feraheme caused decreased fetal weights and fetal malformations at maternally toxic doses of 13-15 times the human dose. Use Feraheme during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rats, administration of Feraheme at maternally toxic doses during organogenesis, i.e., daily doses approximately 2 times the recommended 510 mg human dose (on a mg/m² basis) for 12 days, caused a decrease in fetal weights. The cumulative animal exposure was approximately 13 times the human therapeutic course of 1.02 g (on a mg/m² basis). In rabbits, administration of Feraheme at maternally toxic doses during organogenesis, i.e., daily doses approximately 2 times the recommended 510 mg human dose (on a mg/m² basis) for 14 days, was associated with decreased fetal weights and external and/or soft tissue fetal malformations. The cumulative animal exposure was approximately 15 times the human therapeutic course of 1.02 g on a mg/m² basis [see *Nonclinical Toxicology* (13.3)].

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 [see Contraindications (4)].

10.1 Nonclinical Data

No macroscopic or microscopic signs of toxicity and no changes in the clinical pathology data related to toxicity were observed following single intravenous doses of Feraheme up to 450 mg iron/kg in rats (approximately 10 times the recommended 510 mg human dose on a mg/m² basis) and in dogs (approximately 33 times the recommended 510 mg human dose on a mg/m² basis).

11 DESCRIPTION

Feraheme is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethyl ether. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of Feraheme is $\text{Fe}_{5874}\text{O}_{8752}\cdot\text{C}_{11715}\text{H}_{18682}\text{O}_{9923}\text{Na}_{414}$ 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

Feraheme was not tested for carcinogenic effects. In standard genotoxicity tests, Feraheme 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. Feraheme had no effect on male or female fertility or general reproductive performance in rats.

13.2 Animal Toxicology and Pharmacology

Animal studies demonstrate that the plasma half-life of Feraheme increased with increasing dose. The highest tissue concentrations of Feraheme were found in the liver, spleen, and central lymph node pool; administered radiolabeled Feraheme (⁵⁹Fe) was found in the red blood cell fraction by 24 hr. Studies with radiolabeled drug product demonstrated that renal elimination of the iron in Feraheme was insignificant, while the carbohydrate coating was significantly excreted in the urine and feces.

Repeat-dose toxicity studies with Feraheme up to 12 mg Fe/kg/day for 13 weeks in rats (cumulative exposure approximately 12 times the anticipated exposure of a human therapeutic course of 1.02 g of Feraheme on mg/m² basis) and dogs (cumulative exposure approximately 40 times the anticipated exposure of a human therapeutic course of 1.02 g of Feraheme on mg/m² basis) demonstrated dose-dependent decreases in body weight gain and food consumption, and increases in pigmentation intensity. No systemic toxicity or immunotoxicity was observed at the relevant clinical doses. Changes in red blood cell counts, hemoglobin and serum iron, increases in liver and spleen weight, and the accumulation of iron-positive pigmentation in various organs were observed as expected with the administration of iron-containing agents.

13.3 Reproductive and Developmental Toxicology

In rats, no maternal or fetal effects of Feraheme were observed at daily doses of 31.6 mg Fe/kg during organogenesis for 12 days, approximately 1 time the recommended human dose of 510 mg (on mg/m² basis). The cumulative animal exposure was approximately 5 times the human therapeutic course of 1.02 g (on a mg/m² basis). Administration of Feraheme during organogenesis at maternally toxic doses of 100 mg Fe/kg/day (daily exposure was approximately 2 times the recommended 510 mg human dose on a mg/m² basis) for 12 days (cumulative exposure was approximately 13 times the human therapeutic course of 1.02 g on a mg/m² basis) caused a decrease in fetal weights.

In rabbits, no maternal or fetal effects of Feraheme were observed at daily doses of 16.5 mg Fe/kg during organogenesis for 14 days, approximately 1 time the recommended human dose of 510 mg (on mg/m² basis). The cumulative animal exposure was approximately 7 times the human therapeutic course of 1.02 g (on a mg/m² basis). Administration of Feraheme during organogenesis at maternally toxic doses of 45 mg Fe/kg/day (daily exposure approximately 2 times the recommended 510 mg human dose on a mg/m² basis) for 14 days (cumulative exposure approximately 15 times the human therapeutic course of 1.02 g on a mg/m² basis) caused decreased fetal weights and external and/or soft tissue fetal malformations.

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)

ENDPOINT	Trial 1 Non-Dialysis CKD		Trial 2 Non-Dialysis CKD		Trial 3 CKD on Dialysis	
	Feraheme n = 226	Oral Iron n = 77	Feraheme n = 228	Oral Iron n = 76	Feraheme n = 114	Oral Iron n = 116
Baseline Hgb (mean $\pm$ SD, g/dL)	9.9 $\pm$ 0.8	9.9 $\pm$ 0.7	10.0 $\pm$ 0.7	10.0 $\pm$ 0.8	10.6 $\pm$ 0.7	10.7 $\pm$ 0.6
Hgb change from Baseline at Day 35 (mean $\pm$ SD, g/dL)	1.2* $\pm$ 1.3	0.5 $\pm$ 1.0	0.8* $\pm$ 1.2	0.2 $\pm$ 1.0	1.0* $\pm$ 1.1	0.5 $\pm$ 1.1
Baseline TSAT (mean $\pm$ SD, %)	9.8 $\pm$ 5.4	10.4 $\pm$ 5.2	11.3 $\pm$ 6.1	10.1 $\pm$ 5.5	15.7 $\pm$ 7.2	15.9 $\pm$ 6.3
TSAT change from Baseline at Day 35 (mean $\pm$ SD, %)	9.2 $\pm$ 9.4	0.3 $\pm$ 4.7	9.8 $\pm$ 9.2	1.3 $\pm$ 6.4	8.4 $\pm$ 12.6	0.6 $\pm$ 8.3
Baseline ferritin (mean $\pm$ SD, ng/mL)	123.7 $\pm$ 125.4	146.2 $\pm$ 136.3	146.1 $\pm$ 173.6	143.5 $\pm$ 144.9	340.5 $\pm$ 159.1	357.6 $\pm$ 171.7
Ferritin change from Baseline at Day 35 (mean $\pm$ SD, ng/mL)	300.7 $\pm$ 214.0	0.3 $\pm$ 82.0	381.7 $\pm$ 278.6	6.9 $\pm$ 60.1	233.9 $\pm$ 207.0	-59.2 $\pm$ 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 ($\pm$ SD) in hemoglobin level from the retreatment baseline for patients with an increase in hemoglobin was 0.86 ($\pm$ 0.68) g/dL and was 0.5 ($\pm$ 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 controlled room temperature (20° to 25°C (68° to 77°F)). Excursions permitted to 15° – 30°C (59° – 86°F).

17 PATIENT COUNSELING INFORMATION

Prior to Feraheme administration:

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



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