PRODUCT MONOGRAPH

PrFERAHEME®

ferumoxytol for injection

30 mg/mL (510 mg/17 mL) elemental iron

Hematinic

FOR INTRAVENOUS USE ONLY

Manufactured by:

AMAG Pharmaceuticals, Inc.
1100 Winter Street
Waltham, MA 02451
USA

Date of Revision:

June 05, 2015

Imported and Distributed by:

Takeda Canada Inc.
435 North Service Road West
Oakville, Ontario L6M 4X8
Canada

Submission Control No: 183454

TABLE OF CONTENTS

FERAHEME®

ferumoxytol for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Sterile aqueous colloidal solution; 30 mg/mL (510 mg/17 mL) elemental iron.	Polyglucose sorbitol-carboxymethylether (PSC), Mannitol, Water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

Geriatrics (>65 years of age):

No overall differences in safety or efficacy were observed with FERAHEME® use between geriatric patients and younger patients (<65 years) in clinical studies. However, post-market surveillance reports suggest elderly patients or patients with multiple co-morbidities who experience a serious hypersensitivity reaction due to FERAHEME® may have more severe outcomes. The potential risks and benefits of FERAHEME® administration should be carefully considered in these patients.

Pediatrics (<18 years of age):

FERAHEME® has not been evaluated in patients less than 18 years of age.

CONTRAINDICATIONS

FERAHEME® is contraindicated in patients with:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Any allergies to other parenteral iron products.
- Any known history of drug allergy.
- Evidence of iron overload.
- Anemia not caused by iron deficiency.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

FERAHEME® is contraindicated in patients with any allergy to this drug or other parenteral iron products or in patients with any known history of drug allergy.

The following are clinically significant adverse events:

- Serious hypersensitivity reactions including life threatening and fatal anaphylaxis/anaphylactoid reactions have been reported in patients receiving intravenous iron products including FERAHEME® (see Immune, Hypersensitivity below).
- Serious cases of hypotension (see Cardiovascular below).

FERAHEME® should only be administered as an intravenous infusion over at least 15 minutes when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions (See Immune, Hypersensitivity below).

Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each infusion of FERAHEME®

Elderly patients (> 65 years of age) or patients with multiple co-morbidities who experience a serious hypersensitivity reaction due to FERAHEME® may have more severe outcomes. The potential risks and benefits of FERAHEME® administration should be carefully considered in these patients.

General

Delivery of FERAHEME®: FERAHEME® should only be administered as an intravenous infusion in 50-250 ml of 0.9% sterile sodium chloride or 5% sterile dextrose over a minimum period of 15 minutes following dilution and **must not** be administered by direct injection of the undiluted product (see DOSAGE AND ADMINISTRATION). The change of administration from a rapid IV injection to an infusion may reduce the risk of serious hypersensitivity reactions including life-threatening and fatal outcomes reported in the post-market setting (see Post-Market Adverse Drug Reactions), and allow healthcare professionals to better intervene at the first signs of prodromal symptoms of hypersensitivity. However, this has not been demonstrated in clinical studies and healthcare professionals are reminded to continue to closely monitor patients during the infusion and for 30 minutes following delivery of each dose of FERAHEME®.

Iron Overload: Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic haemosiderosis. Regularly monitor the haematologic response and iron parameters, such as serum ferritin and transferrin saturation, during parenteral iron therapy. Do not administer FERAHEME® to patients with iron overload (see CONTRAINDICATIONS).

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. Patients with a serum ferritin of >600 ng/mL were not studied in the clinical studies.

Magnetic Resonance (MR) Imaging: Administration of FERAHEME® may transiently affect the diagnostic ability of MR imaging because of its superparamagnetic properties; it is not expected to interfere with other imaging modalities. 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; maximal alteration of vascular MR images is anticipated to be evident for 1-2 days following FERAHEME® administration.

Carcinogenesis and Mutagenesis: 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.

Cardiovascular: Severe adverse reactions of clinically significant hypotension have been reported. In clinical studies, hypotension was reported in 4.7% (125/2656) of patients, including serious events in 0.4% (11/2656) of patients. Hypotension has also been reported in the post-marketing experience. Observe patients for signs and symptoms of hypersensitivity including hypotension during and for at least 30 minutes following each administration.

Immune

Hypersensitivity: FERAHEME® may cause life-threatening and fatal hypersensitivity reactions, including anaphylaxis and/or anaphylactoid reactions. Anaphylactic type reactions presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported in the post-marketing setting, including a cluster of serious reactions reported in Canada (see ADVERSE REACTIONS, Post-market Adverse Drug Reactions). In CKD clinical studies, serious hypersensitivity reactions were reported in 0.2% (3/1642) of patients receiving FERAHEME®. In non-CKD clinical studies, serious hypersensitivity reactions were reported in 0.6% (6/1014) of patients who received FERAHEME®. The combined rate of serious hypersensitivity reactions across the CKD and non-CKD clinical study patient population is 0.3% (9/2656).

Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 7.1% (189/2656) of patients treated with FERAHEME®. In a non-CKD clinical study, moderate to severe hypersensitivity reactions were reported in 2.5% (10/406) of patients treated with FERAHEME® and in 1.0% (2/199) treated with iron sucrose.

Observe patients for signs and symptoms of hypersensitivity during and for at least 30 minutes following each FERAHEME® infusion. Only administer the drug when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

In post-marketing reports, several patients who experienced serious hypersensitivity reactions immediately after treatment with FERAHEME® had documented allergies to other intravenous iron products or other drug allergies. In clinical studies, patients with any allergy to other iron products or multiple (two or more) drug allergies were excluded. These patients may be at

increased risks of hypersensitivity reactions associated with FERAHEME®. FERAHEME® is contraindicated in patients with any allergy to parenteral iron products and in patients with any known history of drug allergy.

Infection: Nonclinical data suggest the risk that all intravenous iron products may be harmful in the presence of severe infection, although a higher incidence of infections has not been observed in randomized clinical trials. Patients with active infections requiring ongoing treatment were excluded from clinical studies with FERAHEME®. Clinicians should consider the potential risk of using FERAHEME® in patients with active systemic infections.

Sexual Function/Reproduction

FERAHEME® had no effect on male or female fertility or general reproductive performance in rats at doses up to 18 mg/kg/day. Dosing of pregnant rats at ≥30 mg/kg/day for 36 days (equal to cumulative total iron exposure of 12 times the human dose on a mg/m^2 basis) during gestation and lactation resulted in delayed sexual maturation and reduced reproductive competence in the offspring (See TOXICOLOGY).

Special Populations

Pregnant Women: There are no studies of FERAHEME® in pregnant women. In rabbits, ferumoxytol administered daily (43 mg/kg) over 14 days resulted in accumulation of iron (602 mg/kg) approximating 14 times the estimated human iron exposure (70 kg human) from a single course of FERAHEME®. Fetal malformations indicating teratogenicity and decreased fetal weights indicating fetotoxicity were observed. These effects were not seen at lower doses (16.5 mg Fe/kg) in either rabbits or rats. Treatment of pregnant rats during gestation resulted in reduced reproductive competence of the offspring (see TOXICOLOGY).

FERAHEME® should not be used during pregnancy; if pregnancy occurs, the patients should be informed of the potential risk. FERAHEME® should not be used in women of childbearing potential not using adequate contraception.

Nursing Women: It is not known whether FERAHEME® is present in human milk. However, 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.

Pediatrics: The safety and effectiveness of FERAHEME® in pediatric patients have not been established.

Geriatrics (>65 years of age): 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. Elderly patients or patients with multiple co-morbidities who experience a serious hypersensitivity reaction due to

FERAHEME® may have more severe outcomes. The potential risks and benefits of FERAHEME® should be carefully considered in these patients.

Monitoring and Laboratory Tests

Patients must have confirmed iron deficiency anemia (IDA) based on appropriate laboratory tests before treatment (see WARNINGS AND PRECAUTIONS, General, Iron Overload).

Regularly monitor the hematologic response (hemoglobin [Hgb], haematocrit) and iron parameters (serum ferritin, transferrin saturation) during parenteral iron therapy. 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.

Monitor patients for signs and symptoms of hypotension following each FERAHEME® administration. Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each 15 minute infusion of FERAHEME®. Any patient who experiences an adverse reaction should be monitored until clinically resolved. In addition, patients should be placed in a reclined or semi-reclined position during infusion and for at least 30 minutes thereafter.

Any patient who experiences an adverse reaction, should be monitored closely until clinically resolved.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

FERAHEME® has resulted in life-threatening and fatal hypersensitivity reactions and in severe clinically significant hypotension (see WARNINGS AND PRECAUTIONS).

In clinical studies, involving 2656 patients, 1642 CKD patients and 1014 non-CKD patients were exposed to FERAHEME®. Of these patients, 32.8% were male and the median age was 57 years (range of 18 to 96 years).

Serious hypersensitivity treatment emergent adverse events (TEAEs) were reported in 0.3% (9/2656) of patients with IDA who received FERAHEME® during the clinical studies. Three of these nine cases were characterized as anaphylactic reactions and one case was characterized as an anaphylactoid reaction. Serious hypotension TEAEs were reported in 0.4% (11/2656) of patients who received FERAHEME® in the clinical trials.

Clinical Trial Adverse Drug Reactions

Across the three randomized clinical trials in patients with chronic kidney disease, 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. Patients received their second FERAHEME® injection 2 to 8 days after the first injection.

Table 1 lists TEAEs reported with an incidence of ≥ 0.5% of CKD patients on FERAHEME®.

Table 1: Treatment Emergent Adverse Events Reported in ≥ 0.5% of CKD Patients on FERAHEME® in Randomized, Active-controlled, Open-label Studies

Adverse Event	FERAHEME® 2 x 510 mg (n = 605)	Oral Iron (n = 280)
MedDRA System Organ Class **Preferred Term**		
General Disorders and Administration Site Conditions		
Asthenia	5 (0.8%)	2 (0.7%)
Chest Discomfort	4 (0.7%)	0
Chest Pain	8 (1.3%)	2 (0.7%)
Fatigue	4 (0.7%)	1 (0.4%)
Infusion site Extravasation	4 (0.7%)	0
Infusion site Swelling	4 (0.7%)	0
Oedema	10 (1.7%)	4 (1.4%)
Peripheral Oedema	12 (2.0%)	9 (3.2%)
Pyrexia	6 (1.0%)	2 (0.7%)
Gastrointestinal disorders		
Abdominal Pain	8 (1.3%)	4 (1.4%)
Constipation	13 (2.1%)	16 (5.7%)
Diarrhea	24 (4.0%)	23 (8.2%)
Nausea	19 (3.1%)	21 (7.5%)
Vomiting	9 (1.5%)	14 (5.0%)
Infections and Infestations		
Bronchitis	4 (0.7%)	1 (0.4%)
Upper Respiratory Tract Infection	5 (0.8%)	1 (0.4%)
Metabolism and Nutrition Disorders		
Dehydration	4 (0.7%)	1 (0.4%)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	6 (1.0%)	0 (0%)
Muscle Spasms	6 (1.0%)	4 (1.4%)
Nervous System Disorders		
Dizziness	16 (2.6%)	5 (1.8%)
Dysgeusia	4 (0.7%)	1 (0.4%)
Headache	11 (1.8%)	6 (2.1%)

Adverse Event	FERAHEME® 2 x 510 mg (n = 605)	Oral Iron (n = 280)
MedDRA System Organ Class **Preferred Term**		
Syncope	5 (0.8%)	1 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	8 (1.3%)	4 (1.4%)
Dyspnoea	6 (1.0%)	3 (2.1%)
Rales	5 (0.8%)	2 (0.7%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	7 (1.2%)	2 (0.7%)
Rash	6 (1.0%)	1 (0.4%)
Vascular Disorders		
Flushing	4 (0.7%)	0
Hypertension	6 (1.0%)	2 (0.7%)
Hypotension	15 (2.5%)	1 (0.4%)

In CKD 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, diarrhoea, dizziness, ecchymosis, pruritus, chronic renal failure, and urticaria.

Following completion of the controlled phase of the trials, 69 CKD 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 fourth randomized, double-blind, placebo-controlled, cross-over safety study in CKD patients, 713 patients were exposed to one dose of 510 mg of ferumoxytol and placebo (IV saline). Table 2 lists TEAEs reported with an incidence of ≥ 0.5% of CKD patients on FERAHEME® and at a greater incidence with FERAHEME® than with placebo.

Table 2: Treatment Emergent Adverse Events Reported in ≥0.5% of CKD Patients on FERAHEME® and at a Greater Incidence with FERAHEME® than with Placebo in a Randomized, Double Blind Study

Adverse Event	FERAHEME® 1 x 510 mg (N=713)	Placebo (N=711)
MedDRA System Organ Class **Preferred Term**		
Cardiac Disorders		
Cardiac Failure Congestive	4 (0.6%)	0
Gastrointestinal Disorders		
Diarrhea	9 (1.3%)	8 (1.1%)
Nausea	10 (1.4%)	8 (1.1%)
Vomiting	10 (1.4%)	6 (0.8%)
General Disorders and Administration Site Conditions	6 (0.8%)	3 (0.4%)
Fatigue	10 (1.4%)	6 (0.8%)
Oedema Peripheral		
Metabolism and Nutrition Disorders		
Hypoglycaemia	4 (0.6%)	0
Musculoskeletal and Connective Tissue Disorders		
Pain in Extremity	4 (0.6%)	1 (0.1%)
Nervous System Disorders		
Dizziness	7 (1.0%)	6 (0.8%)
Headache	8 (1.1%)	7 (1.0%)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea	4 (0.6%)	3 (0.4%)
Wheezing	4 (0.6%)	1(0.1%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	5 (0.7%)	2 (0.3%)
Vascular Disorders		
Hypotension	8 (1.1%)	7 (1.0%)

Post-Market Adverse Drug Reactions

Because these adverse events are spontaneously reported in a voluntary manner from a population of uncertain size, it is not possible to reliably estimate their frequency. The following serious adverse reactions have been reported from the post-marketing spontaneous reports with FERAHEME®: life-threatening and fatal anaphylactic/anaphylactoid reactions, cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, unresponsiveness,

loss of consciousness, heart rate (including tachycardia) and rhythm abnormalities, hypertension, angioedema, ischemic myocardial events, congestive heart failure, hypoxia, dyspnoea, hypersensitivity, back pain, abdominal pain, pulse absent, and cyanosis. These adverse reactions typically occurred within 30 minutes after the administration of FERAHEME®, although some events have occurred up to 1 hour and longer after receiving the drug. Reactions have occurred following the first dose or subsequent doses of FERAHEME®.

In Canada, there has been a cluster of 22 serious hypersensitivity reactions reported from post-marketing spontaneous reports, including two with a fatal outcome. In 6 of these 22 (27%) reactions, drug hypersensitivity was reported in the patient's medical history. In 3 of the 6 (50%) patients, there was a history of allergy for multiple drugs, and in 4 there was a previous allergy to other intravenous iron products. In the remaining 16 patients, information on drug allergies was not reported.

From June 30, 2009 to December 30, 2013, the estimated cumulative reporting rate of serious hypersensitivity reactions in the post-market setting worldwide was 0.03% (240/913,266 doses). In Canada, FERAHEME® has been marketed since the fall of 2012; as of December 30, 2013, the estimated reporting rate of serious hypersensitivity reactions was 0.14% (22/15,732 doses).

DRUG INTERACTIONS

Overview

FERAHEME® may reduce the absorption of concomitantly administered oral iron preparations.

Drug-Drug Interactions

Drug-drug interaction studies with FERAHEME® were not conducted.

Drug-Food Interactions

Interactions with food have not been established. FERAHEME® may reduce the absorption of concomitantly administered oral iron preparations.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Based on limited *in vitro* assessment of interactions of ferumoxytol with laboratory tests requiring colorimetric or photometric quantification, ferumoxytol may interfere with the assays for bilirubin (increase), uric acid (decrease), triglycerides (increase), BUN (possible decrease), calcium (possible increase) and cholesterol (possible decrease). The greatest effect may be observed during the first 48 hours post dose. There may be residual interference for up to several days until ferumoxytol is fully cleared from plasma.

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of FERAHEME® is expressed in terms of mg of elemental iron, with each mL of undiluted FERAHEME® containing 30 mg of elemental iron.

Recommended Dose and Dosage Adjustment

The recommended dose of FERAHEME® is an initial 510 mg intravenous infusion administered over at least 15 minutes. For patients receiving two doses, the second 510 mg intravenous infusion is to be administered 2 to 8 days later (see Administration below).

The administration of FERAHEME® by infusion is intended to reduce the risk of serious hypersensitivity reactions. The recommended dosage of FERAHEME® in IDA patients with CKD is based on the patient's pre-treatment Hgb and body weight as provided in Table 3.

Table 3: Recommended Dosing Table for FERAHEME® Administration (CKD)

	Total Amount of FERAHEME® to Administer mg of Iron (Number of vials)	
Baseline Hgb	**≤ 50 kg Body Weight**	**> 50 kg Body Weight**
> 100-120 g/L	510 mg iron (1 vial)	2 × 510 mg iron (2 vials)
≤ 100 g/L	2 × 510 mg iron (2 vials)	2 × 510 mg iron (2 vials)

For patients receiving haemodialysis, administer FERAHEME® once the blood pressure is stable and the patient has completed at least one hour of haemodialysis. Monitor for signs and symptoms of hypotension following each FERAHEME® infusion.

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

Administration

FERAHEME® (30 mg/mL) should only be administered as an intravenous infusion in 50-250 mL of 0.9% sterile sodium chloride or 5% dextrose over a minimum period of 15 minutes following dilution of a single use vial. Each vial contains 510 mg of elemental iron in 17 mL. The diluted FERAHEME® should be used immediately (within 4 hours).

Patients should be placed in a reclined or semi-reclined position during infusion and for at least 30 minutes thereafter.

Observe patients for signs and symptoms of hypersensitivity for at least 30 minutes following each FERAHEME® infusion. Only administer the drug when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Monitor for signs and symptoms of hypotension during the infusion and for at least 30 minutes following each administration of FERAHEME®.

Any patient who experiences an adverse reaction, should be monitored closely until clinically resolved.

Reconstitution

Volume of FERAHEME®	Volume of 0.9% sodium chloride or 5% dextrose in infusion bag	Approximate final volume (mL)	Nominal concentration (g Fe / mL)
1 vial containing 510 mg elemental Fe in 17 mL	50 mL	67	7.6
	100 mL	117	4.4
	250 mL	267	1.9

OVERDOSAGE

For management of suspected drug overdose, please contact your regional Poison Control Centre.

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).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

FERAHEME® is 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. 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 and incorporation into Hgb.

Pharmacodynamics

Cardiac Electrophysiology: In a randomized, positive- and placebo-controlled, parallel-group study, healthy patients 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). FERAHEME® did not prolong the QTc interval, the QRS duration, or the PR interval in this study. No clinically meaningful effect of FERAHEME® on heart rate was observed.

Pharmacokinetics

The pharmacokinetic (PK) behavior of FERAHEME® has been examined in healthy patients and in patients with CKD stage 5D on haemodialysis. 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 (V_d) 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 V_d 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 haemodialysis.

Special Populations and Conditions

The effect of age on the pharmacokinetics of ferumoxytol has not been assessed. No gender differences in ferumoxytol PK parameters were observed.

STORAGE AND STABILITY

Store at controlled room temperature (20^o - 25^oC [68^o - 77^oF]). Excursions permitted to 15^o – 30^oC (59^o – 86^oF). Protect from light. Protect from freezing.

SPECIAL HANDLING INSTRUCTIONS

For reconstitution, FERAHEME® must only be mixed with sterile sodium chloride 9 mg/ml (0.9%) or sterile 5% dextrose up to a final concentration of 2-8 mg iron per ml stored in polyvinyl chloride or ethylene and propylene intravenous bags. No other intravenous dilution solutions and therapeutic agents should be used.

Shelf-life after first opening and after dilution for infusion:

Based on the shelf life after first opening and after dilution for infusion, the chemical and physical in-use stability has been demonstrated for 96 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would not be longer than 4 hours at 25 °C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FERAHEME® is a black to reddish brown sterile aqueous colloidal solution. Each mL of FERAHEME® contains the equivalent of 30 mg of elemental iron as superparamagnetic iron oxide particles with Polyglucose sorbitol carboxymethylether (PSC) coating in Water for Injection (WFI). Additional PSC and mannitol are added to adjust tonicity and sodium hydroxide may be added to adjust pH. It has low bleomycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, is unbuffered, and has a pH of 6.0 to 8.0.

FERAHEME® is available in single use vials in cartons of 2 or 10 vials.

Not all pack sizes may be marketed.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

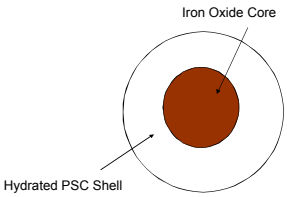
Drug Substance

Common name: ferumoxytol drug substance (iron oxide-PSC complex)

Chemical name: superparamagnetic iron oxide particle with a polyglucose sorbitol carboxymethylether coating

Structural formula:

Sketch of PSC-coated Iron Oxide



Molecular formula:

$(FeO_{1.49})_x(C_{400}H_{638}O_{339})_y$ where x is approximately 5700 and y is approximately 30. The values of x and y were estimated based upon an average chemical composition.

Iron core = $FeO_{1.49}$ and PSC shell is $C_{400}H_{638}O_{339}Na_{14}$

Molecular mass:

Calculated average molecular weight of ferumoxytol = 801435 g/mol.

The apparent molecular weight = (750 kDa)

Physicochemical properties: Ferumoxytol is a black to reddish brown aqueous colloidal solution containing superparamagnetic iron oxide particles with a polyglucose sorbitol carboxymethylether coating.

CLINICAL TRIALS

FERAHEME® for the treatment of iron deficiency anemia in chronic kidney disease (Stages 1-5 and 5D) has been investigated in three pivotal Phase III clinical trials. These three randomized, open-label, controlled, multicenter clinical studies (Studies A, B and C) assessed the efficacy and safety of two 510 mg doses of FERAHEME® relative to oral iron in a total of 923 patients with CKD stages 1-5 and 5D on haemodialysis (including 31 kidney transplant recipients). 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®.

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 daily dose of 200 mg elemental iron daily for 21 days. Trials A and B enrolled patients with non-dialysis dependent CKD and Trial C enrolled patients who were undergoing haemodialysis. Eligibility criteria included patients at least 18 years of age with CKD, Hgb ≤11.0 g/dL (Hgb ≤11.5 g/dL for Study C), TSAT ≤30%, and serum ferritin of ≤600 ng/mL prior to dosing. For patients using ESAs in Studies A and B, the ESA dose was to be stable for at least 10 days prior to dosing and throughout the study. Study C included only patients on haemodialysis for at least 90 days and on stable therapy with ESAs. Exclusion criteria included: active gastrointestinal bleeding or acute bleeding episodes within 4 weeks of treatment; causes of anemia other than iron deficiency; active infections requiring ongoing treatment; and treatment with greater than 35,000 units (25,000 units in Study C) per week of Epogen® (epoetin alfa) or 120 µg Aranesp® (darbepoetin alfa) per 2 weeks. The primary efficacy endpoint assessed the change in Hgb from baseline to Day 35.

Table 4 provides the patient demographics and baseline characteristics for each of the three trials.

Table 4: Patient Demographics and Baseline Characteristics

	Study A Non-Dialysis CKD		Study B Non-Dialysis CKD		Study C CKD on Dialysis	
Mean Age (years)	66		64		60	
Gender (M/F %)	40/60		39/61		57/43	
Race (%): Caucasian	65		58		34	
Black or African-American	32		35		59	
Other	2		7		7	
CKD Stages:						
1 and 2	1%		2%			
3	38%		38%			
4	47%		47%			
5	11%		12%			
5D on haemodialysis					100%	
	FERAHEME® n = 226	**Oral Iron** n = 77	**FERAHEME®** n = 228	**Oral Iron** n = 76	**FERAHEME®** n = 114	**Oral Iron** n = 116
Mean Baseline (±SD) Values:						
Hgb (g/dL)	9.9 ±0.8	9.9 ±0.7	10.0 ±0.7	9.95 ±0.78	10.6 ±0.7	10.7 ±0.6
Serum Ferritin (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
TSAT (%)	9.8 ±5.4	10.4 ±5.2	11.3 ±6.1	10.1 ±5.5	15.7 ±7.2	15.9 ±6.3
Percentage of patients on ESA at baseline	42	44	36	43	100	100

There were no important differences in age, gender, or race by treatment group in Studies A and B, but in Study C there was a difference in the gender distribution between groups (50% males and 50% females for FERAHEME®; 63% males and 36% females for oral iron).

Table 5 presents a summary of the efficacy results. The mean change from baseline in Hgb at Week 5 was statistically significantly greater in the FERAHEME®-treated group than in the oral

iron-treated group in Studies A, B and C. This result was consistent across age, race, and gender subgroups, as well as across subgroups defined by stage of CKD, baseline Hgb, baseline ferritin levels, and use of concomitant medications such as ESAs, angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARB) and anticoagulants.

Table 5: Summary of Efficacy (Intent to Treat Population)

Endpoint	**Study A Non-Dialysis CKD**		**Study B Non-Dialysis CKD**		**Study C CKD on Dialysis**	
	FERAHEME® n = 226	Oral Iron n = 77	FERAHEME® n = 228	Oral Iron n = 76	FERAHEME® n = 114	Oral Iron n = 116
Primary Endpoint:						
Hgb change from baseline at Day 35 (mean±SD, g/dL)	1.2[a] ±1.3	0.5 ±1.0	0.8[a] ±1.2	0.2 ±1.0	1.02[b] ±1.1	0.5 ±1.1
Secondary and Additional Endpoints:						
% Hgb responders at Day 35*	51.8[a]	19.5	39.0[d]	18.4	49.1[b]	25.0
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	412.6[c] ±247.95	4.3 ±48.22	518.1[c] ±331.86	6.5 ±47.16	356.7[c] ±247.12	-37.6 ±107.0
TSAT change from baseline at Day 35 (%)	9.2[c] ±9.37	0.3 ±4.65	9.8[c] ±9.17	1.3 ±6.38	6.4[c] ±12.59	0.6[c] ±8.34

*Hgb responders were defined as a ≥1 g/dL increase in Hgb from baseline.

[a] $p \leq 0.0001$

[b] $p = 0.0002$

[c] $P < 0.0001$

[d] $p = 0.0010$

Efficacy of FERAHEME® in Patients with CKD Stages 1-5 with and without ESA Therapy

In Study A, the mean change from Baseline in Hgb at Day 35 in the FERAHEME® group was significantly greater than in the oral iron group in both patients using ESAs (1.64 vs. 0.86 g/dL; p=0.0052) and patients not using ESAs (0.91 vs. 0.25 g/dL; p<0.0001).

In Study B, the mean change from Baseline in Hgb at Day 35 in the FERAHEME® group was significantly greater than in the oral iron group in patients using ESAs (1.16 vs. 0.19 g/dL; p=0.0010) and patients not using ESAs (0.62 vs. 0.13 g/dL; p=0.0052).

Efficacy of FERAHEME® in Patients Remaining Iron Deficient and Anemic Following the First Course of Treatment

At the end of the randomized phase in all three studies, patients from both FERAHEME® and oral iron groups could enter an optional retreatment phase and receive an open-label course of FERAHEME® as two doses of 510 mg, provided they continued to meet the original study entry criteria. Overall, 69 patients received two additional 510 mg intravenous injections of FERAHEME®. Increases in Hgb at Day 35 after retreatment compared to retreatment baseline were observed in patients previously randomized to FERAHEME® (Study A: 0.31±0.66 g/dL [N=21]; Study B: 0.55±0.89 g/dL [N=22]; Study C: those previously randomized to 2 x 510 mg FERAHEME® (0.56±0.95 g/dL [N=14]), those previously randomized to 4 x 255 mg FERAHEME® (0.68±0.89 g/dL [N=12])).

DETAILED PHARMACOLOGY

Plasma half-life of ferumoxytol increased with increasing dose in rats, but remained constant with increasing doses in dogs. The highest tissue concentrations of ferumoxytol were found in the liver, spleen, and central lymph node pool; administered radiolabeled ferumoxytol (^{59}Fe) was found in the red blood cell fraction by 24 hr. Studies with radiolabeled drug product demonstrated that renal elimination of the iron in ferumoxytol was insignificant, while the carbohydrate coating was significantly excreted in the urine and feces.

TOXICOLOGY

Acute Toxicity

Single dose intravenous injection of ferumoxytol at dose levels up to 450 mg Fe/kg were tolerated in rats and dogs. Treatment-related clinical signs consisted of brown discoloration of skin and/or mucous membranes due to the dark colored test material. Transient paw swelling in rats was attributed to increased vascular permeability (also seen at in rats at high dose levels of 180 and 360 mg/kg for 14 days).

Repeat-Dose Toxicity

Repeat-dose intravenous toxicity studies with ferumoxytol administered daily 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 ferumoxytol on mg/m^2 basis) and dogs (cumulative exposure approximately 40 times the anticipated exposure of a human therapeutic

course of 1.02 g of ferumoxytol on mg/m^2 basis) demonstrated dose-dependent decreases in body weight gain and food consumption, and increases in serum ALT, AST and alkaline phosphatase in rats. Changes in red blood cell counts, Hgb and serum iron, increases in liver and spleen weight, and the prominent accumulation of iron-positive pigmentation in various organs were observed as expected with the administration of iron-containing agents.

Similar findings to those described in 13-week studies were observed in rats and dogs following daily intravenous injection of ferumoxytol up to 37 mg Fe/kg/day for 4 weeks followed by 4- and 26-week treatment-free recovery periods. Iron-staining pigment persisted in organs/tissues following the 26-week recovery period. Liver lesions consisting of focal or multifocal haemorrhage, haemorrhagic necrosis, chronic inflammation and/or bile duct hyperplasia were present following the 26-week recovery period in rats previously administered 18 and 37 mg/kg/day for 4 weeks.

Mutagenicity and Genotoxicity

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.

Carcinogenicity

Ferumoxytol was not tested for carcinogenic effects.

Reproductive and Developmental Toxicology

Ferumoxytol had no effect on male or female fertility or general reproductive function in rats at doses up to 18 mg/kg/day. Dosing of pregnant rats at ≥30 mg/kg/day (12 times the human dose on a mg/m^2 basis based on cumulative exposure over 36 days) during gestation and lactation resulted in delayed sexual maturation and reduced reproductive competence in the offspring.

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 4.2 times (in the rat study) and 5.1 times (in the rabbit study) the estimated human therapeutic dose based on body surface area and cumulative exposures. In rats, administration of ferumoxytol during organogenesis at 13.3 times the estimated human therapeutic dose based on body surface area and cumulative exposure caused a decrease in fetal weights. In rabbits, administration of ferumoxytol during organogenesis at a minimally maternally toxic dose of 45 mg Fe/kg/day for 14 days, resulting in cumulative exposure approximating 14 times the estimated human therapeutic dose of 1.02 g based on body surface area, caused external and/or soft tissue fetal malformations, and decreased fetal weights. These fetal malformations included dome-shaped head, incomplete ossification of the skull, malrotated limbs, flexed front paws, microglossia and cleft palate, hydrocephaly and anencephaly.

In a pre and postnatal development toxicity study in rats, treatment of the pregnant dams (the F_0 generation) with ferumoxytol during gestation and lactation caused decreased maternal body

weight and food consumption observed during gestation and lactation. The no-adverse-effect-level (NOAEL) for the F_0 generation was 30 mg/kg/day (cumulative exposure approximately 12 times the human therapeutic dose of 1.02 g on a mg/m^2 basis). The NOAEL for maternal delivery, neonatal development and survival, and pup (F_1 generation) behaviour, learning and memory was found to be 60 mg/kg/day. Treatment of F_0 females at 60 mg/kg delayed sexual maturation in the F_1 males and decreased their reproductive competence. Treatment of pregnant F_0 females at dose levels of 30 and 60 mg/kg/day produced disruption of the estrous cycle and decreased reproductive competence in the F_1 females The NOAEL was 10 mg/kg/day (cumulative exposure approximately 4 times the human therapeutic course of 1.02 g on a mg/m^2 basis) for F_1 growth based on significantly decreased neonatal body weights during weaning, and for F_1 female reproductive competence. The NOAEL for reproductive competence is 30 mg/kg/day for the F_1 males. A lactation study showed that radiolabeled ferumoxytol showed minimal distribution of either ^{59}Fe or ^{14}C radioactivity into milk.

Toxicology of PSC

The polyglucose sorbitol carboxymethylether (PSC) coating of ferumoxytol caused transient paw swelling in rats similar to Feraheme, at doses of 400 mg/kg/day and higher. In lungs of rats, PSC-related microscopic findings included alveolar histiocytosis, perivascular lymphocyte infiltrate, chronic inflammation, and hemorrhage over a 14 day study. Dose-related increases in the incidence and severity of alveolar histiocytosis were observed in animals given 400, 800, or 1600 mg/kg/day of PSC (equal to cumulative PSC exposures of 62, 124, and 249 times the human equivalent dose on a mg/m^2 basis respectively). Dogs experienced intestinal inflammation following administration of PSC at 15, 120, 375, and 750 mg/kg/day (cumulative PSC exposures of 8, 62, 194, and 389 times the human equivalent dose on a mg/m^2 basis respectively) but not when treated with vehicle control. Both rats and dogs had dose-dependent increased vacuolation (vacant spaces) in the renal tubules of the kidneys, starting at 375 mg/kg/day in dogs and 400 mg/kg/day in rats.

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PART III: CONSUMER INFORMATION

PrFERAHEME®
Ferumoxytol for injection
For Intravenous Use Only

This leaflet is part III of a three-part "Product Monograph" published when FERAHEME® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is only a summary and will not tell you everything about FERAHEME®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
FERAHEME® is used for treating adult patients with reduced kidney function who have anemia resulting from lack of stored iron (iron deficiency anemia) caused by chronic kidney disease (CKD).

What it does:
FERAHEME® replenishes your body's iron. Iron is a key part of your red blood cells that carry oxygen throughout your body.

When it should not be used:
FERAHEME® should not be used if:
- You are allergic to FERAHEME® or other iron products given by injection or infusion
- You have any known history of drug allergy
- You have iron overload
- Your anemia is not caused by iron deficiency

What the medicinal ingredient is:
Ferumoxytol (iron)

What the nonmedicinal ingredients are:
- Polyglucose sorbitol carboxymeththylether (PSC)
- Mannitol
- Water for Injection (WFI)

What dosage form it comes in:
Sterile injection solution in single dose vials. Each vial contains 510 mg/17 mL or 30 mg/mL elemental iron.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

FERAHEME® should not be used in patients allergic to this drug or other iron products given by injection or infusion or in patients with any know history of drug allergy.

Serious side effects with the use of FERAHEME® are:
- **Allergic reactions including life-threatening and fatal allergic reactions (anaphylaxis)**
- **Severe low blood pressure**

FERAHEME® should only be given as an intravenous infusion over at least 15 minutes in a setting where appropriate personnel and therapies for the treatment of severe allergic reactions are also available.

Patients should be closely monitored for signs and symptoms of allergic reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each infusion of FERAHEME®.

Patients should speak to their doctor before receiving FERAHEME® if they are older than 65 years or have an underlying condition, such as liver or heart disease, as the risk of having severe consequences including death may be higher after a serious allergic reaction.

BEFORE you use FERAHEME® talk to your doctor if:
- You are pregnant or plan to become pregnant. Female patients who can get pregnant should use effective methods of birth control while receiving FERAHEME®. FERAHEME® should not be used in pregnant women.
- You are breastfeeding. Breastfeeding should be stopped while receiving FERAHEME®.
- You have had allergic reactions to other IV irons.
- You need to have a magnetic resonance imaging scan (MRI). Tell your doctor even if you are going to have an MRI within three months after the last dose of FERAHEME®.
- You have any infection.
- You have low blood pressure

FERAHEME® is not recommended for use in patients under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Before using FERAHEME®, tell your doctor or nurse about your other medications including ones you bought without a prescription, vitamin and mineral supplements.

- FERAHEME® may reduce the absorption of oral iron when taken together.
- FERAHEME® may interfere with some laboratory tests.

PROPER USE OF THIS MEDICATION

Usual Dose:
510 mg elemental iron to be given into the vein (intravenous infusion over 15 minutes) usually followed by a second dose of 510 mg elemental iron in 2 to 8 days after.

Patients with milder forms of anemia who weigh less than 50 kg should only receive a single dose of 510 mg of elemental iron.

Your doctor or nurse will administer FERAHEME® by infusion into a vein. You will be lying down and your blood pressure and pulse will be monitored. FERAHEME® will be administered in an environment where any allergic event can receive appropriate and prompt treatment.

You will be carefully observed during the infusion and for at least 30 minutes after each infusion by your doctor or nurse. Please immediately tell the doctor or nurse if you start to feel unwell. They may decide to stop the infusion.

Missed Dose:
If you miss your scheduled dose, call your healthcare professional.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common side effects (≥1% < 10%) following the use of FERAHEME® are:

diarrhoea, nausea, dizziness, low blood pressure, constipation, the swelling of the hands or feet, headache, vomiting, abdominal pain, chest pain, cough, itching, high temperature, back pain, breathing difficulties, rash, high blood pressure, injection site reactions (such as pain, bruising), and muscle cramps.

If these become bothersome, talk to your doctor.

Cases of severe, life threatening and sometimes fatal allergic reactions and cases of severe low blood pressure have been reported with the use of FERAHEME®.

The table below lists serious side effects and provides recommendations to call your doctor as indicated.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	**Low Blood Pressure** – which may be associated with dizziness, lightheadedness, loss of consciousness, chest pain, heart attack		√	√
	Severe Allergic Reaction – Which are sometimes life threatening and associated with difficulty breathing, low blood pressure, itching, rash, loss of consciousness, chest pain, heart attack, flushing		√	√

This is not a complete list of side effects. For any unexpected effects while taking FERAHEME®, contact your doctor or pharmacist.

HOW TO STORE FERAHEME®

Store between 15° – 30°C. Protect from light. Protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

    Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or AMAG Pharmaceuticals, Inc. at 1-877-411-2510 or visit the website at www.amagpharma.com

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