FERUMOXYTOL- ferumoxytol injection
Sandoz Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FERUMOXYTOL INJECTION safely and effectively. See full prescribing information for FERUMOXYTOL INJECTION.

FERUMOXYTOL injection, for intravenous use
Initial U.S. Approval: 2009

WARNING: RISK FOR SERIOUS
HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS

See full prescribing information for complete boxed warning.
Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving ferumoxytol. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiorespiratory arrest.

- **Only administer ferumoxytol as an intravenous infusion over at least 15 minutes and only when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. (5.1)**
- **Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following ferumoxytol infusion including monitoring of blood pressure and pulse during and after ferumoxytol administration. (5.1)**
- **Hypersensitivity reactions have occurred in patients in whom a previous ferumoxytol dose was tolerated. (5.1)**

INDICATIONS AND USAGE

Ferumoxytol is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron (1) or
- who have chronic kidney disease (CKD). (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of ferumoxytol is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. (2)
- Administer ferumoxytol as an intravenous infusion in 50 to 200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes. (2)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Known hypersensitivity to ferumoxytol or any of its components. (4)
- History of allergic reaction to any intravenous iron product. (4)

WARNINGS AND PRECAUTIONS

- Greater risk of anaphylaxis in patients with multiple drug allergies. (5.1)
- Hypotension: Ferumoxytol may cause hypotension. Monitor for signs and symptoms of hypotension following each administration of ferumoxytol. (5.2)
- Iron Overload: Regularly monitor hematologic responses during ferumoxytol therapy. Do not administer ferumoxytol to patients with iron overload. (5.3)
- Magnetic Resonance Imaging Test Interference: Ferumoxytol can alter magnetic resonance imaging (MRI) studies. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (≥ 2%) are diarrhea, headache, nausea, dizziness, hypotension, constipation, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS with ferumoxytol injection, contact Sandoz Inc., at 1-800-525-8747, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS

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

- **Only administer ferumoxytol as an intravenous infusion over at least 15 minutes and only when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions***[see **Warnings and Precautions (5.1)**].*
- **Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following ferumoxytol infusion including monitoring of blood pressure and pulse during and after ferumoxytol administration***[see **Warnings and Precautions (5.1)**].*
- **Hypersensitivity reactions have occurred in patients in whom a previous ferumoxytol dose was tolerated***[see **Warnings and Precautions (5.1)**].*

1 INDICATIONS AND USAGE

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

- who have intolerance to oral iron or have had unsatisfactory response to oral iron or
- who have chronic kidney disease (CKD).

2 DOSAGE AND ADMINISTRATION

The recommended dose of ferumoxytol injection is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer ferumoxytol as an intravenous infusion in 50 to 200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes. Administer while the patient is in a reclined or semi-reclined position.

Ferumoxytol injection does not contain antimicrobial preservatives. Discard unused portion. Ferumoxytol injection, when added to intravenous infusion bags containing either 0.9% Sodium Chloride Injection, USP (normal saline), or 5% Dextrose Injection, USP, at concentrations of 2 to 8 mg elemental iron per mL, should be used immediately but may be stored at controlled room temperature (25°C ± 2°C) for up to 4 hours or refrigerated (2 to 8° C) for up to 48 hours

The dosage is expressed in terms of mg of elemental iron, with each mL of ferumoxytol containing 30 mg of elemental iron. Evaluate the hematologic response (hemoglobin,

ferritin, iron and transferrin saturation) at least one month following the second ferumoxytol infusion. The recommended ferumoxytol injection dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

For patients receiving hemodialysis, administer ferumoxytol 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 ferumoxytol infusion.

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Ferumoxytol is contraindicated in patients with:

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Hypersensitivity Reactions

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

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

Only administer ferumoxytol as an intravenous infusion over at least 15 minutes and only when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Closely observe patients for signs and symptoms of hypersensitivity including monitoring of blood pressure and pulse during and after ferumoxytol administration for at least 30 minutes and until clinically stable following completion of each infusion *[see Adverse Reactions (6.2)*].

In a clinical study in patients with IDA, regardless of etiology, hypersensitivity reactions

were reported in 0.4% (4/997) of subjects receiving ferumoxytol administered as intravenous infusion over at least 15 minutes. These included one patient with severe hypersensitivity reaction and three patients with moderate hypersensitivity reactions.

In clinical studies predominantly in patients with IDA and CKD, serious hypersensitivity reactions were reported in 0.2% (4/1,806) of subjects receiving ferumoxytol (administered as a rapid intravenous injection – prior method of administration no longer approved). Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.5% (63/1,806) of these subjects.

In the post-marketing experience, fatal and serious anaphylactic type reactions presenting with cardiac/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of ferumoxytol may have more severe outcomes *[see Boxed Warning*, *Adverse Reactions (6.2) and Use in Specific Populations (8.5)].*

5.2 Hypotension

Ferumoxytol may cause clinically significant hypotension.

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

In clinical studies in patients with IDA and CKD, hypotension was reported in 1.9% (35/1,806) of subjects, including three patients with serious hypotensive reactions, who had received ferumoxytol as a rapid intravenous injection (prior method of administration no longer approved).

Hypotension has also been reported in the post-marketing experience *[see Adverse Reactions (6.2)].* Monitor patients for signs and symptoms of hypotension following each ferumoxytol 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 ferumoxytol to patients with iron overload.

In the 24 hours following administration of ferumoxytol, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in the ferumoxytol complex.

5.4 Magnetic Resonance (MR) Imaging Test Interference

Administration of ferumoxytol may transiently affect the diagnostic ability of MR imaging. Conduct anticipated MR imaging studies prior to the administration of ferumoxytol. Alteration of MR imaging studies may persist for up to 3 months following the last ferumoxytol dose. If MR imaging is required within 3 months after ferumoxytol administration, use T1- or proton density-weighted MR pulse sequences to minimize the

ferumoxytol effects; MR imaging using T2-weighted pulse sequences should not be performed earlier than 4 weeks after the administration of ferumoxytol. Maximum alteration of vascular MR imaging is anticipated to be evident for 1 to 2 days following ferumoxytol administration *[see Clinical Pharmacology (12.3)].*

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

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

The data described below reflect exposure to ferumoxytol in 997 patients exposed to a 1.02 g course of ferumoxytol administered as two 510 mg intravenous (IV) doses: 992 subjects (99.5%) received at least 1 complete dose of ferumoxytol and 946 subjects (94.9%) received 2 complete doses. The mean cumulative IV Iron exposure was 993.80 ±119.085 mg.

The safety of ferumoxytol was studied in a randomized, multicenter, double-blind clinical trial in patients with IDA (IDA Trial 3), [see Clinical Studies (14.1)]. In this trial, patients were randomized to two intravenous infusions of 510 mg (1.02 g) of ferumoxytol (n=997), or two intravenous infusions of 750 mg (1.500 g) of ferric carboxymaltose (FCM) (n=1000). Both intravenous irons were infused over a period of at least 15 minutes. Most patients received their second infusion of ferumoxytol and FCM 7(+1) days after Dose 1.

The mean (SD) age of the study population (N=1997) was 55.2 (17.16) years. The majority of patients were female (76.1%), white (71.4%) and non-Hispanic (81.8%). The mean (SD) hemoglobin at baseline for all patients was 10.4 (1.5) g/dl.

Serious adverse events were reported in 3.6% (71/1997) of ferumoxytol-and FCM-treated patients. The most common (≥2 subjects) serious AEs reported in ferumoxytol-treated patients were syncope, gastroenteritis, seizure, pneumonia, hemorrhagic anemia, and acute kidney injury. In FCM-treated patients the most common (≥2 subjects) serious AEs were syncope, cardiac failure congestive, angina pectoris, and atrial fibrillation.

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

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

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

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

Across two clinical trials in patients with IDA (IDA Trial 1 and 2), *[see Clinical Studies (14.1)],* patients were randomized to: two injections (rapid intravenous injection -prior method of administration no longer approved) of 510 mg of ferumoxytol (n=1,014), placebo (n=200), or five injections/infusions of 200 mg of iron sucrose (n=199). Most patients received their second ferumoxytol injection 3 to 8 days after the first injection. Adverse reactions related to ferumoxytol and reported by ≥ 1% of ferumoxytol-treated patients in these trials were similar to those seen in Trial 3.

In Trials 1 and 2, adverse reactions leading to treatment discontinuation and occurring in ≥ 2 ferumoxytol-treated patients included hypersensitivity (0.6%), hypotension (0.3%), and rash (0.2%).

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

Across three randomized clinical trials in patients with IDA and CKD (CKD Trials 1, 2, and 3), *[see Clinical Studies (14.2)],* a total of 605 patients were exposed to two injections of 510 mg of ferumoxytol and a total of 280 patients were exposed to 200 mg/day of oral iron for 21 days. Most patients received their second ferumoxytol injection 3 to 8 days after the first injection.

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

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

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

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

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

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following serious adverse reactions have been reported from the post-marketing experience with ferumoxytol: fatal, life-threatening, and serious anaphylactic-type reactions, acute myocardial ischemia with or without myocardial infarction or with in-stent thrombosis in the context of a hypersensitivity reaction, cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, unresponsiveness, loss of consciousness, tachycardia/rhythm abnormalities, angioedema, ischemic myocardial events, congestive heart failure, pulse absent, and cyanosis. These adverse reactions have usually occurred within 30 minutes after the administration of ferumoxytol. Reactions have occurred following the first dose or subsequent doses of ferumoxytol.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal adverse reactions

Severe adverse reactions including circulatory failure (severe hypotension, shock including in the context of anaphylactic reaction) may occur in pregnant women with parenteral iron products (such as ferumoxytol) which may cause fetal bradycardia, especially during the second and third trimester.

Data

Animal Data

Administration of ferumoxytol during organogenesis, at doses of 31.6 mg Fe/kg/day in rats and

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

approximately 6 times the estimated human daily dose based on body surface area, was associated with external and soft tissue fetal malformations and decreased fetal weights.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of ferumoxytol in pediatric patients (less than 18 years old) have not been established.

8.5 Geriatric Use

In controlled clinical trials, 833 patients ≥ 65 years of age were treated with ferumoxytol. No overall differences in safety and efficacy were observed between older and younger patients in these trials, but greater sensitivity of older individuals cannot be ruled out. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients with multiple or serious co-morbidities who experience hypersensitivity reactions and/or hypotension following administration of ferumoxytol may have more severe outcomes. The potential risks and benefits of ferumoxytol administration should be carefully considered in these patients *[see Dosage and Administration (2), Warnings and Precautions (5.1), and Clinical Studies (14)].*

10 OVERDOSAGE

Limited data are available regarding overdosage of ferumoxytol in humans.

Excessive dosages of ferumoxytol may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer ferumoxytol to patients with iron overload *[Warnings and Precautions (5.3)].*

Ferumoxytol is not removed by hemodialysis.

11 DESCRIPTION

Ferumoxytol is an iron replacement product containing ferumoxytol for intravenous infusion. Ferumoxytol is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is 17 to 31 nm in diameter. The chemical formula of ferumoxytol is $Fe_{5874}O_{8752}$-$C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa.

Ferumoxytol injection is a sterile aqueous colloidal product that is formulated with

mannitol. It is a reddish brown liquid, and is provided in single-dose vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of ferumoxytol injection contains 30 mg of elemental iron and 44 mg of mannitol, and 30 mg polyglucose sorbitol carboxymethylether. The formulation is isotonic with an osmolality of 270 to 330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ferumoxytol 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 ferumoxytol (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 ferumoxytol on QT interval durations. No clinically meaningful effect of ferumoxytol on heart rate was observed.

12.3 Pharmacokinetics

The pharmacokinetic (PK) behavior of ferumoxytol has been examined in healthy subjects and in patients with CKD stage 5D on hemodialysis. Ferumoxytol 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 ferumoxytol. 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 ferumoxytol 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 ferumoxytol PK parameters. No gender differences in ferumoxytol PK parameters were observed. Ferumoxytol is not removed by hemodialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ferumoxytol was not tested for carcinogenic effects. In standard genotoxicity tests, ferumoxytol showed no evidence of mutagenic activity in an *in vitro* Ames test or clastogenic activity in either an *in vitro* chromosomal aberration assay or an *in vivo* micronucleus assay.

No adverse effects on fertility or general reproductive performance were noted in animal studies. Ferumoxytol had no effect on male or female fertility or general reproductive function in rats. In a pre and postnatal development study in rats, intravenous administration of ferumoxytol from gestation day 6 until lactation day 20 at doses up to 60 mg/kg/day (approximately 3 times the daily human dose based on body surface area comparisons assuming a 60-kg person) had no effect on maternal delivery or numbers of liveborn offspring. Male offspring (F1) of pregnant rats (F0) administered ferumoxytol at a dose of 60 mg/kg/day had delayed sexual maturation and decreased reproductive competence. Female offspring (F1) of pregnant rats (F0) administered ferumoxytol at doses of 30 mg/kg/day or 60 mg/kg/day had delayed sexual maturation and decreased reproductive competence. Doses of 30 mg/kg/day and 60 mg/kg/day are approximately 2 and 3 times the daily human dose based on body surface area comparisons assuming a 60-kg person, respectively.

14 CLINICAL STUDIES

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

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

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

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

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

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

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

	IDA Trial 1		IDA Trial 2	
	Ferumoxytol N = 608	Placebo N = 200	Ferumoxytol N = 406	Iron Sucrose

ENDPOINT				N = 199
Baseline Hgb mean (SD), g/dL	8.9 (0.9)	8.8 (0.9)	8.9 (0.9)	8.8 (1.0)
Proportion of patients with Hgb Increase of ≥2 g/dL at any time from Baseline to Week 5, %	81.1	5.5	84	81.4
Treatment Difference (%, 95% CI)	75.6* (71.2, 80)		2.6 (-3.9, 9.1)	
Mean change in Hgb from Baseline to Week 5 mean (SD), g/dL	2.6 (1.5)	0.1 (0.9)	2.9 (1.6)	2.7 (1.3)
Proportion of patients with Hgb ≥12 g/dL at any time from Baseline to Week 5, %	50.5	3	66.7	48.2
Baseline TSAT mean (SD) , %	7 (12.9)	5.4 (4.9)	6.1 (9.9)	5.5 (10.3)
Mean change in TSAT from Baseline to Week 5 mean (SD), %	11.4 (15.1)	0.4 (5.8)	15.7 (16.8)	11.9 (14.4)

* p≤0.001 for main efficacy endpoint

In IDA Trial 1, fatigue-related symptoms and impacts were assessed using a patient reported outcome instrument, FACIT-Fatigue (score range from 0 to 52 with higher scores indicating less fatigue). After 5 weeks, ferumoxytol-treated patients reported greater improvement from baseline in the fatigue score (+11.7 ± 11.73 points) than did

patients in the placebo arm (+6.8 ± 9.51 points) with a treatment difference of 4.9 (95% CI: 3.08-6.71) points.

The safety of ferumoxytol in IDA patients with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used was also assessed in another randomized, multicenter, double-blind safety clinical trial (IDA Trial 3). Patients were randomized in a 1:1 ratio to either two infusions of 510 mg (1.020 g) of ferumoxytol (n=997) or two infusions of 750 mg (1.500 g) of ferric carboxymaltose (FCM) (n=1000). Both IV irons were infused over a period of at least 15 minutes. Most patients received their second infusion of ferumoxytol or FCM 7(+1) days after the first infusion. This study included patients with any etiology of IDA including CKD excluding dialysis-dependent CKD.

In IDA Trial 3, the mean age of patients was 55 years (range, 18 to 96); 76% were female; 71% were Caucasian, 24% were Black, 3% were Asian, and 2% were other races.

The study met the primary endpoint to demonstrate non-inferiority to FCM with respect to the percentage of patients who experienced moderate-to-severe hypersensitivity reactions (including anaphylaxis) or moderate-to-severe hypotension (ferumoxytol: 0.6%; FCM: 0.7%; treatment difference: -0.1%; exact 95% confidence interval: -0.91% to +0.70%).

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

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

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

* Adjusted for difference in baseline Hgb

In IDA Trial 3, the incidence of severe hypophosphatemia (defined by blood phosphorous of <0.6 mmol/L at week 2) in the patients receiving ferumoxytol (0.4% of

patients) was less than those receiving FCM (38.7% of patients).

14.2 Iron Deficiency Anemia in Patients with Chronic Kidney Disease

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

The safety and efficacy of ferumoxytol for the episodic treatment of iron deficiency anemia in patients with CKD were assessed in three randomized, open-label, controlled clinical trials (CKD Trial 1, 2 and 3) where ferumoxytol was administered as a rapid intravenous injection (prior method of administration - no longer approved). These trials also included an uncontrolled, follow-up phase in which patients with persistent iron deficiency anemia could receive two additional 510 mg intravenous injections of ferumoxytol. The major efficacy results from the controlled phase of each study are shown in Table 5.

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

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

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

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

Table 5 shows the Baseline and mean change to Day 35 in hemoglobin (Hgb, g/dL), transferrin saturation (TSAT, %) and ferritin (ng/mL) in each treatment group for Trial 1, 2, and 3.

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

ENDPOINT	CKD Trial 1 Non-Dialysis		CKD Trial 2 Non-Dialysis		CKD Trial 3 Dialysis	
	Ferumoxytol N = 226	Oral Iron N = 77	Ferumoxytol N = 228	Oral Iron N = 76	Ferumoxytol N = 114	Oral Iron N = 116
Baseline	9.9 (0.8)	9.9	10 (0.7)	10	10.6 (0.7)	10.7(0.6)

Hgb mean (SD), g/dL		(0.7)		(0.8)		
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)	1* (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)	381.7 (278.6)	6.9 (60.1)	233.9 (207)	-59.2 (106.2)

* $p \leq 0.001$ for main efficacy endpoint

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

In a randomized, controlled clinical trial of 162 IDA patients with CKD (92 Non-Dialysis and 70 on Dialysis), mean change in hemoglobin from Baseline to Week 5 was 0.71 ±1.03 g/dL for ferumoxytol-treated patients and 0.61 ±0.97 g/dL for iron sucrose-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Ferumoxytol injection is available in single-dose vials in the following package sizes (**Table 6**).

Table 6: Ferumoxytol Packaging Description

NDC Code	Dose/Total volume per vial	Vials/Carton
NDC 0781-3154-01	510 mg/17 mL	1
NDC 0781-3154-95	510 mg/17 mL	10

16.2 Stability and Storage

Store at 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

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

Prior History of Allergies to Parenteral Iron Products

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

Hypersensitivity Reactions

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

Manufactured in Slovenia by

Lek Pharmaceuticals d.d for

Sandoz Inc., Princeton, NJ 08540

PATIENT INFORMATION
Ferumoxytol Injection
(FER-ue-MOX-i-tol)

What is the most important information I should know about ferumoxytol injection?
Ferumoxytol injection may cause serious side effects including:

- **Serious allergic reactions that can lead to death.** Serious allergic reactions have happened in people after receiving the first dose of ferumoxytol injection or after receiving additional

doses in people who did not previously have an allergic reaction. If you have a history of allergies to many different medicines, you may have an increased risk of serious allergic reactions to ferumoxytol injection. **Tell your healthcare provider or get medical help right away if you get any of these signs or symptoms:**

- rash
- itching
- dizziness or lightheadedness
- swelling of the tongue or throat
- wheezing or trouble breathing

See **"What are the possible side effects of ferumoxytol injection?"** for more information about side effects.

What is ferumoxytol injection?

Ferumoxytol injection is a prescription medicine used to treat iron deficiency anemia in adults who have:

- intolerance to oral iron or who have not responded well to treatment with oral iron or
- chronic kidney disease (CKD).

It is not known if ferumoxytol injection is safe and effective in children less than 18 years of age.

Who should not receive ferumoxytol injection?

Do not receive ferumoxytol injection if you:

- are allergic to **ferumoxytol injection** or any of the ingredients in **ferumoxytol injection**. See the end of this leaflet for a complete list of ingredients in **ferumoxytol injection**.
- have had an allergic reaction to any iron medicine given into your vein by intravenous (IV) infusion.

Before receiving ferumoxytol injection, tell your healthcare provider about all of your medical conditions, including if you:

- have allergies to many different medicines.
- have iron overload
- have low blood pressure (hypotension).
- are pregnant or plan to become pregnant. It is not known if ferumoxytol injection will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ferumoxytol passes into your breast milk. You and your healthcare provider should decide if you will receive ferumoxytol injection or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ferumoxytol injection?

- Ferumoxytol injection will be given to you into your vein by intravenous (IV) infusion over at least 15 minutes by your healthcare provider. You will receive ferumoxytol injection in 2 doses 3 to 8 days apart.
- Your healthcare provider will watch you during and for at least 30 minutes after you receive ferumoxytol injection.

What are the possible side effects of ferumoxytol injection?
Ferumoxytol injection can cause serious side effects, including:

- See **"What is the most important information I should know about ferumoxytol injection?"**
- **Low blood pressure (hypotension)** is a common side effect of ferumoxytol injection and can sometimes be serious. Your healthcare provider will check you for signs and symptoms of hypotension after each ferumoxytol infusion.
- **Iron overload**. Your healthcare provider will do blood tests to check your iron levels during treatment with ferumoxytol injection.

The most common side effects of ferumoxytol injection include: diarrhea, headache, nausea, dizziness, constipation, and swelling of your legs, feet, arms, or hands.
These are not all of the possible side effects of ferumoxytol injection. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ferumoxytol injection.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ferumoxytol injection that is written for health professionals.

What are the ingredients in ferumoxytol injection?
Active ingredient: ferumoxytol
Inactive ingredient: mannitol

Manufactured in Slovenia by
Lek Pharmaceuticals d.d for
Sandoz Inc., Princeton, NJ 08540
For more information, call 1-800-525-8747.

The Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2020

PRINCIPAL DISPLAY PANEL

NDC 0781-3154-01

Ferumoxytol

Injection

510 mg elemental iron

Per 17 mL (30 mg/mL)

For Intravenous Use only

Single-Dose Vial - Discard Unused Portion

Rx only

SANDOZ

FERUMOXYTOL

ferumoxytol injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-3154
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FERUMOXYTOL NON-STOICHIOMETRIC MAGNETITE (UNII: CLH5FT6412) (FERUMOXYTOL NON-STOICHIOMETRIC MAGNETITE - UNII:CLH5FT6412)	FERUMOXYTOL NON-STOICHIOMETRIC MAGNETITE	510 mg in 17 mL

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	748 mg in 17 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-3154-01	1 in 1 CARTON	07/15/2021	
1		17 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		
2	NDC:0781-3154-95	10 in 1 CARTON	07/15/2021	
2		17 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206604	07/15/2021	

Labeler - Sandoz Inc (005387188)

Revised: 6/2022 Sandoz Inc