Intravenous iron side-by-side comparison

Updated October 2022

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	Brand name (generic name)					
	INFeD (iron dextran)[a]	**Ferrlecit (sodium ferric gluconate)[b]**	**Venofer (iron sucrose)[c]**	**Feraheme (ferumoxytol)[d]**	**Injectafer (ferric carboxymaltose)[e]**	**MonoFerric (ferric derisomaltose)[f]**
Manufacturer	AbbVie • Generic: Yes • Novaplus: No	Sanofi • Generic: Yes • Novaplus: Yes	American Regent • Generic: No • Novaplus: Yes	AMAG • Generic: Yes • Novaplus: No	American Regent • Generic: No • Novaplus: No	Pharmacosmos Therapeutics Inc • Generic: No • Novaplus: No
Approval date	1974	1999	2000	2009	2013	2020
Anticipated LOE[g]	Not applicable	Not applicable	Not applicable	Not applicable	2026	2032
Properties						
Carbohydrate shell	Dextran polysaccharides	Gluconate	Sucrose	Polyglucose sorbitol carboxymethyl ether	Carboxymaltose	Derisomaltose
Molecular weight (Da)	165,000	289,000-444,000	34,000-60,000	750,000	150,000	155,000
Potential for labile iron release[h]	-	+++	+/-	-	-	-
Test dose	Yes (0.5 mL)	No	No	No	No	No
Elemental iron concentration (mg/mL)	50	12.5	20	30	50	100
pH	4.5-7	7.7-9.7	10.5-11	6-8	5-7	5-7
Vial volume (mL)	2	5	2.5, 5, 10	17	2, 15, 20 *The 2 mL and 20mL vials are not commercially available and do not currently have an estimated release date.*	1, 5, and 10
Preservative	No	Benzyl alcohol (9 mg/mL)	No	No	No	No

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FDA-approved indications	IDA treatment in patients ≥ 4 mo in whom oral administration is unsatisfactory or impossible	IDA treatment in patients ≥ 6 y with HDD-CKD who are receiving epoetin therapy	• IDA treatment in adult patients with HDD-CKD, NDD-CKD, or PDD-CKD • IDA maintenance in pediatric patients ≥ 2 y with HDD-CKD, NDD-CKD, or PDD-CKD	IDA treatment in adult patients: • Who are intolerant of or have an unsatisfactory response to oral iron • With CKD	• IDA treatment in adult and pediatric patients ≥ 1 y who are intolerant of or have an unsatisfactory response to oral iron • IDA treatment in adults with NDD-CKD	IDA treatment in adult patients: • Who are intolerant of or have an unsatisfactory response to oral iron • With NDD-CKD
Approval in specific populations						
CKD	Yes	HDD	HDD, NDD, PDD	HDD, NDD	NDD	NDD
Oncology	Yes	Published data (off label)	Published data (off label)	Yes	Yes	Yes
Pediatrics	Yes; treatment	Yes; treatment	Yes; maintenance	Published data (off label)	Yes; treatment	No
Adult dosage						
Total iron dose per course of therapy	1,000 mg (off label)	1,000 mg	1,000 mg	1,020 mg	• ≥ 50 kg: 15 mg/kg up to 1,000 mg as a single-dose or 1,500 mg in 2 divided doses • < 50 kg: 15 mg/kg	• ≥ 50 kg: 1,000 mg • < 50 kg: 20 mg/kg
No. of doses to administer total dose	10	8	10 (HDD), 5 (NDD), 3 (PDD)	2	1 or 2	1
No. of days between doses	--	Consecutive dialysis sessions	Consecutive dialysis sessions (HDD), 5 doses over 14 d (NDD), 3 doses over 28 d (PDD)	3 to 8 d	≥ 7 d (with 2-dose regimen)	Not applicable

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Approved dose of elemental iron per administration	100 mg	125 mg	100 mg (HDD), 200 mg (NDD), 300 or 400 mg (PDD)	510 mg	• ≥ 50 kg: 750 mg (2-dose regimen); 15 mg/kg up to 1,000 mg (single-dose regimen) • < 50 kg: 15 mg/kg (may repeat if IDA reoccurs)	• ≥ 50 kg: 1,000 mg • < 50 kg: 20 mg/kg (may repeat if IDA reoccurs)
Max off-label dose per administration	1,000 mg TDI[h]	250 mg[i]	300 mg[j], 500 mg[k]	1,020 mg TDI[l]	1,000 mg[m-q]	1,000 mg
Pediatric dosage	Consult prescribing information	1.5 mg/kg of elemental iron per dialysis session. Do not exceed 125 mg per dose.	0.5 mg/kg every 2 wk (HDD) or every 4 wk (NDD, PDD) for 12 wk	Not applicable	Patients < 50 kg: 15 mg/kg divided in 2 doses separated by ≥ 7 d per course	Safety and effectiveness have not been established in pediatric patients
Adult administration						
IV injection	Undiluted, administer at a rate not to exceed 50 mg per min	Undiluted, administer at a rate of 12.5 mg per min	HDD, NDD: Undiluted, administer over 2-5 min	Not applicable	Undiluted, administer 750 mg dose at rate of 100 mg (2 mL) per min; administer 1,000 mg dose over 15 min	Not applicable
IV infusion	TDI, off-label: dilute in 250 mL of NS, administer over 1 h	Dilute 125 mg in 100 mL of NS, administer over 1 h per dialysis session	• HDD, NDD: Dilute 100 mg (HDD) or 200 mg (NDD) in no more than 100 mL NS; administer over 15 min • PDD: Dilute dose in no more than 250 mL NS; administer 300 mg over 1.5 h for 2 doses, then 400 mg over 2.5 h	Dilute 510 mg in 50-200 mL NS or D5W, administer over 15 min.	Dilute up to 1,000 mg in no more than 250 mL NS such that the concentration is not < 2 mg/mL of elemental iron, administer over ≥ 15 min	Draw appropriate volume of FDI and dilute in 100 mL to 500 mL of NS such that the concentration is > 1 mg/mL of elemental iron, administer over ≥ 20 min

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Other	IM: Inject into muscle mass of upper outer quadrant of the buttock	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Pediatric administration	• IV injection: Undiluted, 50 mg per min • IM injection: Inject into the muscle mass of upper outer quadrant of the buttock • TDI, off-label: 100-< 400 mg doses: dilute in 100 mL of NS; 400-1,000 mg doses: dilute in 250 mL of NS	IV infusion: Dilute dose in 25 mL of NS, administer over 1 h per dialysis session.	• IV injection (HDD, NDD, PDD): Undiluted, administer over 5 min • IV infusion (HDD, NDD, PDD): Diluted in NS at a concentration of 1 to 2 mg/mL, administered over 5-60 min	Not applicable	• IV injection: Undiluted, 100 mg per min (doses ≤ 750 mg) • IV infusion: Dilute dose in NS to a concentration of 2 to 4 mg/mL; administer over ≥ 15 min	Safety and effectiveness have not been established in pediatric patients
Safety						
Contraindications	All anemias not associated with iron deficiency; hypersensitivity	Hypersensitivity to any component	Hypersensitivity to any component	Hypersensitivity to any component; allergic reaction to IV iron	Hypersensitivity to any component	Hypersensitivity to any component
Boxed warning	Yes	No	No	Yes	No	No
Warnings/precautions	• Anaphylactic reactions: Fatal anaphylactic reactions may occur. Use test dose. • Delayed reactions: Large IV doses, such as used with TDI, may be associated with delayed events that	• Hypersensitivity, hypotension: Monitor for signs and symptoms of hypersensitivity and of hypotension during and after administration. • Iron overload: Monitor hematological responses; do not	• Hypersensitivity, hypotension: Monitor for signs and symptoms of hypersensitivity and hypotension during and after administration. • Iron overload: Monitor hematological responses; do not	• Greater risk of anaphylaxis in patients with multiple drug allergies. • Hypotension: Monitor for signs and symptoms of hypotension after each administration.	• Hypersensitivity, hypertension: Monitor for hypersensitivity reactions and hypertension during and after each injection. • Symptomatic hypophosphatemia: Monitor serum phosphate levels in	• Hypersensitivity: Monitor patients for signs and symptoms of hypersensitivity during and after FDI for ≥ 30 min and until clinically stable following infusion.

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	have an onset in 24-48 h after administration. • Patients with underlying conditions: Use cautiously with liver impairment, CV disease, or in patients with a history of multiple allergies and/or asthma. Do not use in acute phase of infectious kidney disease. • Carcinogenesis: May be carcinogenic if administered IM. • Unwarranted use can result in iron overload.	administer to patients with iron overload. • Benzyl alcohol toxicity: Premature and low-birth-weight infants may be more likely to develop toxicity.	administer to patients with iron overload.	• Iron overload: Monitor hematological responses; do not administer to patients with iron overload. • MRI test interference: May alter MRI studies for up to 3 mo following last dose.	patients at risk for low serum phosphate who require a repeat course of treatment. • Laboratory assays may overestimate serum iron and transferrin bound iron if measured within 24 h following administration.	• Do not administer FDI to patients with iron overload.
MRI test interference[r]	• Not mentioned in product labeling but interference may be possible. Consider waiting 1 mo since last dose prior to MRI.	• Not mentioned in product labeling but interference may be possible. Consider waiting 1 wk since last dose prior to MRI.	• Not mentioned in product labeling but interference may be possible. Consider waiting 1 wk since last dose prior to MRI.	• MRI test interference described in product labeling. May alter MRI studies for up to 3 mo following last dose.	• Not mentioned in product labeling but interference may be possible. Consider waiting 1 wk since last dose prior to MRI.	• Not mentioned in product labeling but interference may be possible.
Adverse events	Most common are flushing, dizziness, fever, headache, pain, nausea, vomiting, metallic taste, diaphoresis. Delayed	Most common are: • Adults (incidence ≥ 10%): nausea, vomiting and/or diarrhea, site reaction,	Most common are: • Adults (incidence ≥ 2%): diarrhea, nausea, vomiting, headache, dizziness,	Most common are (incidence ≥ 2%) diarrhea, headache, nausea, dizziness, hypotension,	Most common are • Adults (incidence ≥ 2%): nausea, hypertension, flushing,	Most common are (incidence ≥ 1%) rash and nausea

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	reactions can occur 1-2 d after treatment	hypotension, cramps, hypertension, dizziness, dyspnea, chest pain, leg cramps and pain • Pediatrics 6-15 y (incidence ≥ 10%): hypotension, headache, hypertension, tachycardia, vomiting	hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection-site reactions, chest pain, peripheral edema • Pediatrics (incidence ≥ 2%): headache, respiratory tract viral infection, peritonitis, vomiting, pyrexia, dizziness, cough, nausea, arteriovenous fistula thrombosis, hypotension, hypertension	constipation, peripheral edema	hypophosphatemia, dizziness • Pediatrics (incidence ≥ 4%): hypophosphatemia, injection-site reactions, rash, headache, and vomiting	
Storage and stability						
Intact vials	20°-25°C	20°-25°C	20°-25°C	20°-25°C	20°-25°C	20°-25°C
Syringe	Not applicable	Not applicable	Undiluted (20 mg/mL) or diluted (2-10 mg/mL) are stable for 7 d at room temperature and under refrigeration.	Not applicable	Not applicable	Not applicable
Infusion bag	--	Use immediately	Infusion bag: Diluted (1-2 mg/mL) solution is stable for 7 d at room temperature	Solutions diluted (2-8 mg/mL) in NS or D5W: Use immediately, but may be stored at room temperature (25°C ±	Diluted solution (2-4 mg/mL): Stable for 72 h at room temperature	Diluted solution (1 mg/mL): Stable for 8 h at room temperature

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				2°C) for up to 4 h or refrigerated (2°-8°C) for up to 48 h		
How supplied	Single-use vial (50 mg/mL): 2 mL	Single-use vial (12.5 mg/mL): 5 mL	Single-use vial (20 mg/mL): 2.5 mL, 5 mL, 10 mL	Single-use vial (30 mg/mL): 17 mL	Single-use vial (50 mg/mL): 2, 15 mL, 20 mL *(only 15 mL vial is currently marketed; no release date for the 2 mL or 20 mL vial sizes is available at this time)*	Single-use vial (100 mg/mL): 1 mL, 5 mL, 10 mL
Insurance considerations						
Coverage[s]	Not listed on many payer's formulary coverage lists. Prior authorization likely required.	Not listed on many payer's formulary coverage lists. Prior authorization likely required.	Not listed on many payer's formulary coverage lists. Prior authorization likely required.	Not listed on many payer's formulary coverage lists. Prior authorization likely required.	Not listed on many payer's formulary coverage lists. Prior authorization likely required.	Not listed on many payer's formulary coverage lists. Prior authorization likely required.
Patient assistance program[s]	Yes	No	Yes	Yes	Yes	Yes
Comparative iron trials						

1. ***Am J Kidney Dis*. 1999;33(3):464-470**.[t] Based on adverse event data obtained from Germany and Italy between 1992 and 1996, the reporting rate of allergic reactions was 3.3 episodes per million doses sold for SFG. A similar quantity of iron dextran (all formulations) was sold in the U.S during 1995 and the reporting rate of allergic reactions was 8.7 episodes per million doses. Between the years 1976 and 1996, 74 reports of allergic-type reactions to SFG were submitted in Germany and Italy and 196 reports of allergic-type reactions to iron dextran (all formulations) were submitted to the World Health Organization. The case-fatality rate, based on submissions, was 0 for SFG and 15.8% for iron dextran ($P < .001$).
2. ***Am J Nephrol.* 2000;20(6):455-462**.[u] A retrospective review of all in-center chronic HDD-CKD patients receiving iron dextran was conducted for 1992 through 1997. During the first 4 years of the review period, only LMWD was available; during the last year of the review period, only HMWD was available. Adverse events were identified through documentation or by discontinuation of iron dextran. A total of 33 AEs were identified during 21 courses of IV iron administration. The number of AEs per 100 IV iron courses was 3.2 with LMWD versus 9.1 with HMWD. Compared with LMWD, the OR for an adverse event was significantly increased with HMWD (2.6; 95% CI, 1.2-5.7; $P = .017$). Two anaphylactoid reactions occurred, one in each group.
3. ***Am J Kidney Dis*. 2001;37(4):743-749**.[v] Over a 6-month period, 165 suspected adverse drug events were filed among 841,252 iron dextran administrations at Fresenius Medical Care North America facilities, which represented an AE rate of approximately 20 per 100,000 doses administered. The most common AEs reported were dyspnea (43%), hypotension (23%), and chest pain (19%). Overall, 11% of patients required hospitalization; there was 1 death. Risk of an AE was 8.12 times higher with HMWD than with LMWD.

4. ***Nephrol Dial Transplant*. 2001;16(6):1239-1244**.[w] In a prospective, open-label trial, 55 patients on hemodialysis for at least 3 months and epoetin therapy for at least 4 months with Hgb 9-12 g/dL and serum ferritin 100-600 mcg/L were randomized to receive IS 250 mg once monthly or SFG 62.5 mg once weekly for 6 months. After 6 months of maintenance treatment, there was no significant difference between IS and SFG in Hgb (11.43 ± 1.6 vs. 11.42 ± 0.9), transferrin saturation (33.3% vs. 34.4%), or ferritin (650 ± 293 vs. 650 ± 235). Epoetin requirements were lower, but not significantly, in the iron sucrose group. No AEs or anaphylactoid reactions occurred.
5. ***Kidney Int*. 2002;61(5):1830-1839**.[x] Incidence of drug intolerance, defined as any event that would preclude further administration, was significantly lower in HDD-CKD patients receiving a single 125-mg dose of SFG over 10 min compared with a historic iron dextran control group (0.44% vs. 2.47%, respectively; *P* < .0001), but higher versus placebo (0.44% vs. 0.1%, respectively; *P* = .02). There was a lower incidence of life-threatening events with SFG compared with iron dextran (0.04% vs. 0.61%, respectively; *P* = .001). Iron dextran formulation was not reported.
6. ***Nephrol Dial Transplant.* 2004;19(6):1571-1575.**[y] Between the years 1998-2000, the absolute rates of serious AEs (anaphylaxis, allergic reaction, facial edema, pruritus, urticaria, back pain, cardiac arrest, chest pain, tachycardia, hypotension, dyspnea, respiratory depression, nausea, vomiting, sweating) reported to the FDA MedWatch program were 57.9, 49.6, and 16.6 per million doses of 100 mg of HMWD, SFG, and LMWD, respectively. Compared with LMWD, AEs were significantly increased among recipients of HMWD (OR: 5.5; 95% CI, 4.9-6) and SFG (OR: 6.2; 95% CI, 5.4-7.2).
7. ***Nephron Clin Pract*. 2005;99(4):c97-c101**.[z] Patients with IDA and HDD-CKD were randomized to receive IS (100 mg twice weekly for 2 months and once weekly thereafter, n = 22) or SFG (62.5 mg twice weekly for 2 months and once weekly thereafter, n = 26). After 6 months of therapy, the Hgb was 9.6 ± 0.89 g/dL and 9.3 ± 0.88 with IS and SFG, respectively *(P* =.256). Transient pruritus was documented in 2 and 3 patients in the IS and SFG groups, respectively.
8. ***Nephrol Dial Transplant*. 2005;20(7):1443-1449**.[aa] The all-event AE reporting rates to the FDA MedWatch program between January 1997 and September 2002 were 29.2, 10.5, and 4.2 reports per million 100-mg dose equivalents for iron dextran, SFG, and IS, respectively, while the corresponding all-fatal-event reporting rates were 1.4, 0.6, and 0.0. The reporting rates for urticaria were 2.1, 0.8, and 0.32 reports per million 100 mg dose equivalents for iron dextran, SFG, and IS, respectively; anaphylactoid reaction reporting rates were 0.87, 0.46, and 0.0. For iron dextran, the reporting rates for anaphylaxis and upper airway angioedema were 0.6 and 0.87 per million 100 mg dose equivalents, respectively, and for SFG, the corresponding rates were 0.46 and 0.0. No reports of anaphylaxis or upper airway angioedema were submitted for IS during the review period.
9. ***Nephrol Dial Transplant*. 2006;21(2):378-382.**[bb] Between the years 2001 and 2003, the absolute rate of life-threatening events (death, cardiac arrest, coma, anaphylactoid reaction) spontaneously reported to the FDA MedWatch was 0.6, 0.9, 3.3, and 11.3 per million 100 mg doses of iron dispensed for IS, SFG, LMWD, and HMWD, respectively. Life-threatening events increased, but not significantly, with LMWD compared with IS (OR: 0.2; 95% CI, 0.1-0.4) and SFG (OR: 0.3; 95% CI, 0.1-0.7). There was no significant difference in event rate between IS and SFG (OR: 0.6; 95% CI, 0.2-1.7). HMWD was associated with a significantly greater incidence of life-threatening events compared with LMWD (OR: 3.4; 95% CI, 2-5.9).
10. ***Renal Fail*. 2007;29(4):423-426**.[cc] In a double-blind study, 60 patients with late-stage renal insufficiency (HDD-CKD, PDD-CKD, or NDD-CKD) were randomized to receive LMWD or IS. All patients received a 25 mg test dose of the assigned study drug, followed by the remaining 75 mg if no reaction occurred. The incidence of pruritus, dyspnea, chest pain, nausea, hypotension, swelling, diarrhea, and headache did not differ between groups. Late reactions occurred in 1 patient in each group: headache in the iron dextran group and diarrhea in the IS group.
11. ***Transfusion Altern Transfusion Med*. 2007;9(1):37-42**.[dd] Two studies evaluated the comparative safety of LMWD and IS. In a retrospective, observational study, 8 reactions were documented over 2,294 doses of LMWD and 5 reactions were documented over 2,111 doses of IS. No episodes of anaphylaxis occurred. In a prospective, cross-over trial, 39 stable hemodialysis patients receiving IS were switched to LMWD for 6 months and then were switched back to IS for 6 months. After crossing over from IS to LMWD, there were no differences in Hgb, ferritin levels, or epoetin dose. A total of 13 reactions in 8 patients were reported; 8 and 4 reactions occurred during the LMWD and IS periods, respectively. No anaphylactic reactions occurred.
12. ***Ren Fail*. 2008;30(6):629-638**.[ee] In an open-label, randomized trial, the rates of SAEs per 100 patients were 6.195, 1.818, and 0.862 for LMWD, SFG, and IS, respectively. The SAE rate did not differ significantly between LMWD and SFG, but was significantly lower in the IS group compared with the LMWD group *(P* = .034).
13. ***Am J Health Syst Pharm*. 2012;69(4):310-320**.[ff] Adverse events related to IV iron that were reported to the FDA's Adverse Event Reporting System between October 2009 and June 2010 were classified into 4 categories: death, serious, other major, and other (nonallergic events). The calculated AE rates per million units sold for all categories combined were 5.25, 745.76, 6.85, and 27.08 for IS, ferumoxytol, SFG, and all iron dextran, respectively. The calculated AE rates per million 100 mg iron dose equivalents were 5.24, 146.67, 10.99, and 27.46 for IS, ferumoxytol, SFG, and all iron dextran, respectively. Compared with IS, both ferumoxytol (OR: 142.15; *P*

< .0001) and iron dextran (OR: 5.16; *P* < .0001) had significantly higher rates of all reported AEs. Similarly, compared with SFG, ferumoxytol (OR: 108.85; *P* < .05) and iron dextran (OR: 3.95; *P* < .0001) had significantly higher rates of all reported AEs.

14. ***Am J Hematol*. 2012;87(11):E123-124**.[gg] A retrospective review of all NDD-CKD adult patients who received IV iron between 2008 and 2010 was conducted at a single integrated delivery network. During the review period, 619 unique patients received 3,174 infusions of IV iron. LMWD and HMWD were administered as a 25-mg test dose, followed by the full dose, which was typically given as a 1 to 2 gram TDI. SFG was administered as a 125 mg dose per session and IS was administered as a 200 to 400 mg dose per session. The incidence of reported AEs was 2.5% (3/121), 44.4% (4/9), 3.6% (14/393), and 11.5% (11/96) in the LMWD, HMWD, SFG, and IS groups, respectively. In comparison with LMWD, the OR for experiencing an AE was significantly higher with IS (5.668; 95% CI, 1.508-21.302). All adverse events were mild to moderate intensity and no anaphylactoid or serious reactions were reported during the review period.
15. ***JAMA*. 2015;314(19):2062-2068**.[hh] In a retrospective, new-user cohort study of IV iron recipients (n = 688,183) enrolled in Medicare Part A and B between January 2003 and December 2013, the cumulative risk of anaphylaxis per 1 gram of iron administered was compared for dextran and nondextran IV iron products and among individual IV iron products in patients not on dialysis. There were 274 anaphylaxis cases identified at first exposure. The risk of anaphylaxis at first exposure was 68 per 100,000 persons (95% CI, 57.8-78.7 per 100,000) for iron dextran (HMWD and LMWD) and 24 per 100,000 persons (95% CI, 20.0-29.5 per 100,000) for non–iron dextran (adjusted OR: 2.6; 95% CI, 2.0-3.3; *P* < .001). Compared with IS, anaphylaxis at first exposure was significantly increased with iron dextran (OR: 3.6; 95% CI, 2.4-5.4), SFG (OR: 2.0; 95% CI, 1.2-2.5), and ferumoxytol (OR: 2.2; 95% CI, 1.1-4.3). After first exposure, another 170 anaphylaxis cases were identified. The cumulative anaphylaxis risk per 100,000 was highest with iron dextran and lowest with IS.
16. ***Nephrol Dial Transplant*. 2015;30(12):2068-2075**.[ii] Between July 2009 and December 2011, 265 U.S. small-chain or independent hemodialysis centers that adopted predominant use of ferumoxytol (≥ 90% of IV iron administrations) were matched 1:3 to facilities (n = 795) with predominant use of IS or SFG based on facility type, chain status, and geographic region. During the observation period, 3,752 patients initiated hemodialysis at ferumoxytol-predominant facilities and 10,454 at IS/SFG-predominant facilities. Compared with patients who initiated dialysis at an IS/SFG facility, patients at ferumoxytol facilities had similar incidences of all-cause mortality (HR: 0.95; 95% CI, 0.85-1.07), CV mortality (HR: 0.99; 95% CI, 0.83-1.19), and mortality from infectious causes (HR: 0.88; 95% CI, 0.61-1.25) based on death files in the U.S. Renal Data System. Based on ICD-9 diagnosis codes, the rates of CV events (myocardial infarction, stroke, and CV mortality) and infectious hospitalization were similar for all iron preparations.
17. ***PLoS One*. 2017;12(1):e0171098**.[jj]The safety of ferumoxytol and nonferumoxytol IV iron preparations (IS, SFG, dextran) was compared in a retrospective (2010-2012) cohort study that examined outcomes on the day of or the day following IV iron administration in new users who were selected from a 20% sample of paid Medicare Part A and B claims. In the non-CKD cohort (n = 26,050), there were no significant differences between ferumoxytol and other iron preparations with regard to the rate of hypersensitivity symptoms (HR: 1.04; 95% CI, 0.94-1.16), hypotension (HR: 0.83; 95% CI, 0.52-1.34), the combined endpoint of ED encounters or hospitalizations for CV events (HR: 0.92; 95% CI, 0.51-1.64), anaphylaxis (HR: 1.00; 95% CI, 0.43-2.34), and death (HR: 2.00; 95% CI, 0.33-11.97). Ferumoxytol was associated with a lower risk of all-cause hospitalization, all-cause ED encounters, and the combined endpoint of all-cause ED encounters or hospitalizations. In the NDD-CKD cohort (n = 24,493), there were no significant differences in hypersensitivity symptoms, hypotension, all-cause hospitalization, or the combined endpoint of ED encounters or hospitalizations for CV causes. Ferumoxytol was associated with lower risk of all-cause ED encounters and hospitalizations.

Pivotal ferumoxytol trials

1. ***J Am Soc Nephrol*. 2008;19(8):1599-1605**.[kk] Adult patients with CKD stages 1-5 and IDA were randomized 3:1 to receive open-label treatment with ferumoxytol, administered as 2 doses of 510 mg within 5 ± 3 days (n = 228) or 200 mg of elemental iron daily administered orally for 21 days (n = 76). At day 35, the mean increase in Hgb was 0.82 ± 1.24 g/dL versus 0.16 ± 1.02 g/dL in the ferumoxytol and oral iron groups, respectively (*P* < .0001). Ferumoxytol-treated patients experienced significant increases in Hgb compared with oral iron–treated patients in the subgroup that received ESAs (1.16 ± 1.49 g/dL vs. 0.13 ± 0.93 g/dL; P = .0010) and in the subgroup that did not receive ESAs (0.62 ± 1.02 g/dL vs. 0.13 ± 0.93 g/dL; *P* = .0045). Treatment-related AEs occurred in 10.6% of ferumoxytol-treated patients versus 24% of oral iron-treated patients. Hypotension and HSRs were not observed.
2. ***Clin J Am Soc Nephrol*. 2009;4(2):386-393**.[ll] Adult patients with HDD-CKD, a stable ESA dose, and a Hgb measurement ≤ 11.5 g/dL were randomized 1:1 to receive open-label treatment with ferumoxytol, administered as 2 doses of 510 mg within 5 ± 3 days (n = 114) or 200 mg of elemental iron daily administered orally for 21 days (n = 116). Based on pill count, the mean cumulative dose of oral iron was 3,765 mg. At day 35, the mean increase in Hgb was 1.02 ± 1.13 g/dL versus 0.46 ± 1.06 g/dL in the ferumoxytol and oral iron groups, respectively *(P* = .0002). Significantly more ferumoxytol-treated patients had an increase in Hgb of at least 1 g/dL at day

35 compared with patients receiving oral iron (49.0% vs. 25%; *P* = .0002). Treatment-related AEs occurred in 8.2% versus 15.9% of the ferumoxytol- and oral iron–treated patients, respectively. During the randomized period, 1 patient in the ferumoxytol group had an SAE of hypotension.

3. **IDA-301 trial. *Am J Hematol*. 2014;89(1):7-12**.[mm] Patients with a history of IDA and either an unsatisfactory response to or intolerance of oral iron were randomized in a 3:1 fashion to receive double-blind treatment with ferumoxytol 1.02 grams, delivered as 2 doses of 510 mg, separated by 2 to 8 days (n = 606), or matching placebo (n = 200). An increase in Hgb of at least 2.0 g/dL was achieved in 81.1% of ferumoxytol-treated patients versus 5.5% of placebo-treated patients *(P* < .0001). The mean change in Hgb from baseline to week 5, the alternate primary endpoint, was 2.7 g/dL versus 0.1 g/dL in the ferumoxytol and placebo groups, respectively *(P* < .0001). Adverse events that were considered to be related to ferumoxytol administration were nausea (2.3%), headache (1.8%), hypersensitivity (1.3%), and dizziness (1.3%). In the ferumoxytol group, HSR and anaphylaxis occurred at rates of 0.3% and 0.2%, respectively.
4. ***Am J Hematol.* 2016;91(2):E3-5**.[nn] (Open-label extension of *Am J Hematology*. 2014; 89(1):7-12) Patients who continued to meet the definition of IDA (Hgb < 11 g/dL and TSAT < 20%) during a 6-month observation period were enrolled in a single-arm, open-label extension study. Of the original 808 participants, 634 patients received at least 1 dose of ferumoxytol during the extension phase. For patients originally randomized to placebo (n = 151), the first treatment course of ferumoxytol administered during the open-label extension significantly increased Hgb, by a mean of 2.6 g/dL from baseline *(P* < .0001). Among placebo-treated patients who received a second treatment course or ferumoxytol-treated patients who received a second dose during the open-label phase (n = 244), ferumoxytol significantly increased Hgb, by 1.5 g/dL from baseline *(P* < .0001). Those who received a third treatment course (n = 69) also experienced a significant (1.1 g/dL) increase in Hgb from baseline *(P* < .0001). Overall, 8.9% of patients experienced a related TEAE and 1 patient experienced a TEAE of special interest (HSR or hypotension).
5. **IDA-302 trial. *Am J Hematol*. 2014;89(6):646-650**.[oo] Patients with a history of IDA and either an unsatisfactory response to or intolerance of oral iron were randomized 2:1 to receive open-label treatment with ferumoxytol 1.02 grams, delivered as 2 doses of 510 mg, separated by 5 days (n = 406) or IS 1 gram, delivered as 5 doses of 200 mg on nonconsecutive days during a 14-day period (n = 199). An increase in Hgb of at least 2.0 g/dL was achieved in 84% and 81.4% of ferumoxytol- and IS-treated patients, respectively, at any time during the 5-week follow-up period (treatment difference: 2.58%; 95% CI, -3.9 to 9.1%), which met the predefined criteria for noninferiority. Change in Hgb from baseline to week 5 was significantly greater in the ferumoxytol group compared with the IS group (2.7 mg/dL vs 2.4 mg/dL; *P* = .0124). Changes from baseline to week 5 in patient-reported outcomes (FACIT-Fatigue, SF-36-Vitality, and LASA-Energy) were similar between treatment groups. Drug-related TEAEs occurred in 14.3% and 16.1% of ferumoxytol- and IS-treated patients, respectively.
6. ***Clin J Am Soc Nephrol*. 2014;9(4):705-712**.[pp] Patients with HDD- or NDD-CKD and IDA were randomized to receive open-label treatment with ferumoxytol 1.02 grams (delivered as 2 injections of 510 mg within 5 ± 3 days; n = 80) or IS 1 gram (dosed as 100 or 200 mg over 5 or 10 administrations within 2 to 3 weeks; n = 82). Ferumoxytol was noninferior to iron sucrose at a noninferiority margin of -0.5 mg/dL for the mean change in Hgb from baseline to week 5 (difference: 0.1; 95% CI, -0.21 to 0.41). Ferumoxytol was associated with a greater increase in Hgb at every assessed time point, although the difference between groups was only significant at weeks 2 and 3. One ferumoxytol-treated patient experienced an anaphylactic reaction and 5 IS-treated patients experienced 6 hypotensive events. Iron sucrose was associated with greater rates of hypotension and parosmia than ferumoxytol.
7. **IDA-304 trial. *Am J Hematol*. 2018;93(5):683-690**.[qq] Patients aged 18 years and older with IDA and a history of unsatisfactory response to or intolerance of oral iron were randomized 1:1 to receive double-blind treatment with ferumoxytol 1.02 grams (n = 997) or FCM 1.5 grams (n = 1,000), both administered as 2 doses separated by 7 or 8 days. Ferumoxytol was noninferior to FCM for occurrence of the primary safety composite endpoint of moderate-to-severe HSR, including anaphylaxis, or moderate-to-severe hypertension (0.6% vs. 0.7%, respectively) and for the secondary composite endpoint of moderate-to-severe HSR, including anaphylaxis, serious CV events, or death (1.3% vs. 2%, respectively). Ferumoxytol was also noninferior to FCM for the mean change in Hgb from baseline to week 5 (1.4 mg/dL vs. 1.6 mg/dL, respectively) and superior to FCM for the mean change per gram of iron from baseline to week 5 (1.4 mg/dL vs. 1.1 mg/dL, respectively; *P* < .0001). The incidence of the most frequently reported AEs were similar for ferumoxytol and FCM: headache (3.4% vs. 3.1%), nausea (1.8% vs. 3.4%), dizziness (1.5% vs. 1.6%), and fatigue (1.5% vs. 1.2%). The incidence of hypophosphatemia 2 weeks after treatment was higher with FCM (38.7%) than with ferumoxytol (0.4%) and the difference persisted during the 5-week trial period.

Pivotal ferric carboxymaltose trials

1. ***Nephrol Dial Transplant*. 2014;29(4):833-842**.[rr] In an open-label, noninferiority trial, participants with NDD-CKD and IDA were randomized to receive 2 doses of FCM 15 mg/kg (n = 1276) or 5 doses of IS 200 mg (n = 1285). The primary endpoint, the highest mean Hgb value between baseline and day 56, was 1.13 ± 1.04 in the FCM group and 0.92 ± 0.92 in the IS group (95% CI for difference, 0.13-0.28). The criterion for noninferiority was met. The proportion of patients achieving at least a 1.0 g/dL increase in Hgb was significantly greater in the FCM group than the IS group (48.6% vs. 41%, respectively; 95% CI for difference, 3.6%-11.6%). The primary

safety endpoint — a composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, CHF requiring hospitalization or medical intervention, cardiac arrhythmia, and hyper- or hypotension — occurred in 13.7% in the FCM group compared with 12.1% in the IS group. The most common drug-related AEs were nausea (8.6% for FCM vs. 1.6% for IS), hypertension (4.6% vs. 2.0%), flushing (3.0% vs. 0.1%), dizziness (2.4% vs. 1.2%), and dysgeusia (2.4% vs. 1.2%). Nine patients in the FCM group experienced HSRs, versus 2 in the IS group.

2. ***Transfusion*. 2014;54(2):306-315**.[ss] Participants with IDA of multiple etiologies who failed to exhibit a satisfactory response to a 14-day run-in of oral iron (Hgb increase less than 1%, cohort 1) or an inability to tolerate oral iron during the run-in (cohort 2) were randomized to groups A or B (cohort 1) or groups C or D (cohort 2). Patients in groups A (n = 246) and C (n = 253) received 2 doses of FCM 15 mg/kg (up to 750 mg), separated by 7 days. Patients in group B continued oral iron 325 mg 3 times daily for an additional 14 days (n = 253). Patients in group D received IV iron SOC (n = 245). The primary endpoint, mean increase in Hgb from baseline to highest value by day 35 in cohort 1, was significantly greater with FCM than oral iron (1.57 ± 1.19 g/dL vs. 0.80 ± 0.80 g/dL; *P* = .001). The secondary endpoint, a post-hoc analysis of the primary endpoint in cohort 2, was significantly greater with FCM than IV iron SOC (2.90 ± 1.64 g/dL vs. 2.16 ± 1.25 g/dL; *P* = .001). The primary safety endpoint, a composite of all-cause mortality, nonfatal MI, nonfatal stroke, unstable angina requiring hospitalization, CHF, arrhythmias, and hypo- or hypertension, occurred in 3.4% of all FCM-treated patients, 1.58% of oral iron–treated patients, and 4.9% of IV iron SOC–treated patients. Hypersensitivity reactions occurred in 1% and 2.4% of FCM- and IV iron SOC–treated patients, respectively.

Nonpivotal ferric carboxymaltose trials

1. ***Obstet Gynecol*. 2007;110(2 Pt 1):267-278**.[tt] Healthy women who were within 10 days after delivery and had postpartum anemia were randomized to receive FCM (n = 168), administered as weekly infusions of 15 mg/kg, up to the patient's calculated dose, or oral iron 325 mg (n = 169) 3 times weekly for 42 days. The primary endpoint, the proportion of patients with an increase in Hgb of at least 2 g/dL at the end of treatment, occurred in 96.4% versus 94.1% of FCM- and oral iron–treated patients, respectively (95% CI for difference; -2.19% to 6.88%; *P* = .443). Patients assigned to FCM were more likely to experience mild, transient skin disorders such as rash and pruritus, while patients taking oral iron were more likely to experience gastrointestinal effects. FCM-treated patients had a fall in serum phosphate levels that reached nadir by day 14.
2. ***Am J Gastroenterol*. 2008;103(5):1182-1192**.[m] Patients with IBD and IDA were randomized 2:1 to receive open-label FCM (n = 136) or oral iron (n = 60). FCM was administered as a weekly infusion of 1000 mg or 15 mg/kg, depending on body weight. Up to 3 infusions could be administered. Oral iron was administered as a 100 mg of elemental iron twice daily for 12 weeks. The primary endpoint, change in Hgb levels from baseline to week 12 was similar in both treatment groups, with a median increase of 3.7 g/dL (-1.8 to 9.3 g/dL) in the FCM group and 2.8 g/dL (-1.2 to 8.4 g/dL) in the oral iron group. The difference between groups met noninferiority criteria. Erythematous rash and urticaria were more common with FCM than oral iron (6.6% vs. 1.6%).
3. ***Int J Gynaecol Obstet*. 2008;101(1):67-73**.[n] Postpartum women with IDA (n = 268) were randomized 2:1 to receive open-label FCM or oral iron. FCM-treated patients received 1000 mg or 15 mg/kg on day 1 and then up to 2 additional weekly infusions until the patient reached the calculated iron dose. Oral iron was administered as 100 mg of elemental iron twice daily for 12 weeks. In the FCM group, the mean change in Hgb levels from baseline to week 12 was noninferior to the change in the oral iron group (3.37 g/dL vs. 3.29 g/dL, respectively). Adverse reactions considered related to the study drug were experienced by 10.6% and 11.1% of patients in the FCM and oral iron groups, respectively. One patient in the FCM group experienced an HSR.
4. ***Transfusion*. 2009;49(12):2719-2728**.[o] In an open-label study, women with IDA associated with HUB were randomized 1:1 to receive FCM, dosed up to 1,000 mg per administration (n = 228) or oral iron 3 times daily (n = 225). A greater proportion of FCM-treated patients achieved the primary endpoint, an increase in Hgb level of 2 g/dL or more within 42 days (82% vs. 61.8%; 95% CI of treatment difference; 12.2%-28.3%; *P* < .001). Those assigned to receive FCM were more likely to report fatigue, headache, dizziness, dysgeusia, and rash.
5. ***Gastroenterology*. 2011;141(3):846-853**.[uu] In a multicenter, noninferiority trial, patients with mild to moderate IBD and IDA were randomized to receive open-label FCM (n = 244) or IS (n = 241). The primary outcome, the percentage of patients that experienced an increase in Hgb of at least 2 g/dL at week 12, was achieved in 66.1% and 54.1% of FCM and IS-treated patients, respectively (difference: 11.91%; 95% CI, 2.28%-21.31%; *P* =.008). Rash, dermatitis, pruritus, and hypophosphatemia were more common with FCM infusions.
6. ***Nephrol Dial Transplant*. 2011;26(5):1599-1607.**[p] In a multicenter, open-label trial, patients with NDD-CKD and IDA were randomized to receive up to 3 infusions of FCM (n = 147) or oral iron 325 mg 3 times daily for 56 days (n = 103). The maximum dose of the first FCM infusion was 1000 mg; the maximum dose of subsequent infusions was 500 mg. The primary endpoint, an increase of at least 1 g/dL in Hgb, was achieved in 60.4% versus 34.7% in the FCM and oral iron groups, respectively

(P < .001). Adverse events that were possibly or probably related to the study drug were documented in 2.7% of patients in the FCM group and 26.2% in the oral iron group.

7. ***Nephrol Dial Transplant*. 2013;28(4):953-964**.[q] Adult patients with CKD were randomized to receive FCM (n = 254) or SOC (n = 259). In the FCM group, NDD-CKD patients received 15 mg/kg IV up to a maximum dose of 1000 mg; HDD-CKD patients received 200 mg directly into the venous line of the dialyzer. Patients in the SOC group could receive oral or IV iron or no iron. Over 60% of patients in the SOC group received IV iron at a mean dose of 698.7 mg and 561.1 mg in NDD and HDD patients, respectively. Safety was the primary outcome measure. Although significantly more patients in the IV iron SOC subgroup than the FCM group experienced an SAE (9.6% vs. 3.5%; *P* < .02), none were deemed to be related to the study drug. Drug-related AEs in the FCM group were nausea (2.4%); hypertension (1.6%); vomiting, dizziness, flushing (1.2%); and dysgeusia (0.8%). In the SOC group, AEs included nausea and dizziness (0.8%). No hypersensitivity reactions occurred in either treatment group.

Pivotal ferric derisomaltose trials

1. **FERWON-IDA trial. *Am J Hematol*. 2019;94(9):1007-1014**.[vv] Patients aged 18 years and older with IDA caused by different etiologies and a history of unsatisfactory response or intolerance to oral iron or a screening Hgb measurement that was sufficiently low as to require rapid repletion of iron stores were randomized 2:1 to receive open-label treatment with FDI, given as a single dose of 1000 mg over 20 minutes (n = 1009) or IS, given as 200 mg injections, repeated up to 5 times (n = 503). At baseline, the etiology of IDA was gynecological in 50% of patients and gastroenterological in 26% of patients. The occurrence of adjudicated serious or severe HSR reactions on or after the first dose, was low and similar between IV iron groups with 3 events (0.3%; 95% CI, 0.06-0.88) in the FDI group and 2 events (0.4%; 95% CI, 0.05-1.45) in the IS group. FDI was noninferior to IS for the primary efficacy endpoint of change in Hgb from baseline to week 8 (difference between groups: 0; 95% CI, -0.13-0.13); however, the change in Hgb from baseline to weeks 1 and 2 was significantly greater for FDI vs. IS (*P* < .0001) as was the proportion of responders, defined as an increase of Hgb of at least 2 g/dL or greater. By week 4, differences were no longer statistically significant between groups for change from baseline in Hgb or proportion of Hgb responders. The incidence of composite CV adverse events (0.8% for FDI vs. 1.2% for IS) and hypophosphatemia (3.9% for FIM vs. 2.3% for IS) did not significantly differ between groups. The most common AE in both treatment groups was nausea; rash (1.5%) and chest discomfort (1.1%) were reported more frequently in FIM vs. IS groups (0% and 0%, respectively) and dysgeusia (1.8%) and overdose (1.6%) was more common with IS.
2. **FERWON-NEPHRO. *Nephrol Dial Transplant*. 2021;36:111-120**.[ww] Patients aged 18 years and older with CKD (eGFR < 60 mL/min/1.73m^2 or eGFR < 90 mL/min/1.73m^2 and kidney damage and/or intermediate/high risk of cardiovascular disease based on Framingham model), Hgb ≤ 11 g/dL, and s-ferritin ≤ 100 ng/mL (or 300 ng/mL if transferrin saturation ≤ 30%) were randomized 2:1 to receive open-label treatment with FDI, given as a single dose of 1000 mg over 20 minutes (n = 1027) or IS, given as 200 mg injections, repeated up to 5 times (n = 511). The occurrence of adjudicated serious or severe HSR reactions on or after the first dose was low and similar between treatment groups (3 events for FDI (95% CI, 0.06-0.86) vs. 0 events for IS (95% CI, 0.00-0.73)) and the risk difference between irons was not significantly different (risk difference: 0.29%; 95% CI, -0.19-0.77%). Because the upper bound of the CI was less than 3%, the safety objective was met. At week 8, FDI was noninferior to IS for change in Hgb from baseline (difference: 0.08; 95% CI, -0.06-0.23); at weeks 1, 2, and 4, FDI was superior to IS for Hgb change from baseline. The occurrence of adjudicated composite CV events (death due to any cause, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization, CHF requiring hospitalization or medical intervention, arrhythmias, hypertension, hypotension) was significantly greater in the IS group (41 events in 35 patients, 6.9%) vs. the FDI group (55 events in 42 patients, 4.1%; *P* = .025). Hypophosphatemia (3.2% vs. 0.8%; *P* = .004) and rash (0.6% vs. 0.2%) occurred more commonly in the FDI group. Four serious AEs were reported in the FDI group (2 HSRs, 1 acute MI, 1 infusion-related) vs. 1 serious AE in the IS group (pyrexia).
3. **FERWON-EXT trial. *Am J Hematol*. 2020;95(10):E276-279**.[xx] Patients who were originally enrolled in a randomized, open-label, controlled trial that evaluated FDI (PROVIDE, FERWON-IDA, FERWON-NEPHRO) and received a second, single-dose of FDI 1000 mg (n = 102) were followed for 6 months. A total of 7 ADRs were reported in 5/102 (4.9%) patients; all ADRs were considered mild to moderate in severity with no adjudicated serious or severe HSRs. Six events (5.9%) were adjudicated as CV events, but none were related to FDI. Hypophosphatemia (serum phosphorus < 2.0 mg/dL) was reported in 8 of 102 (7.8%) patients; no cases of severe hypophosphatemia occurred. Hemoglobin significantly increased from baseline to week 2, month 3, and month 6 with a peak at month 3.
4. **FERWON safety analysis*. Am J Hematol.* 2021; 96(1):E11-E15**.[yy] In a prespecified combined safety analysis of the FERWON-IDA and -NEPHRO trials, safety was evaluated in 3,050 patients (FDI: 2,036 patients; IS: 1,014 patients). FDI was noninferior to IS for occurrence of adjudicated serious or severe HSRs based on a noninferior margin of 1.5% for the upper bound of the 95% CI (risk difference between groups for occurrence of serious or severe HSRs: 0.10% (95% CI, -0.57-0.48%)). Significantly more IS-treated patients experienced a composite CV event (48 events in 41 patients; 4.1%) vs. FDI-treated patients (63 events in 50 patients; 2.5%; *P* = .018 between groups). The most frequent CV events were hypertension (FDI: 0.6% vs. IS: 1.4%), CHF (FDI: 0.3% vs. IS: 1.1%), and AF (FDI: 0.2% vs. IS:

0.6%). Overall, the occurrence of the most common ADRs, including nausea (1.2% vs. 1.1%), rash (1% vs. 0.1%), and dysgeusia (0.2% vs. 1%) was low and similar between FDI and IS treatment groups, respectively.

5. ***JAMA*. 2020;323(5):432-443**.[zz] In 2 identically designed, open-label, randomized clinical trials, 245 adults aged 18 years and older with study-defined IDA and a history of intolerance or unresponsiveness to oral iron were randomized 1:1 to receive FDI or FCM. FDI was administered as a single dose of 1000 mg on day 0 while FCM was administered as a dose of 750 mg on days 0 and 7. The primary endpoint, incidence of hypophosphatemia, defined as a serum phosphate level < 2.0 mg/dL, that occurred at any time from baseline to day 35 was significantly lower among patients treated with FDI than those treated with FCM (trial A: 7.9% vs. 75%; *P* <.001; trial B: 8.1% vs. 73.7%; *P* < .001). After excluding hypophosphatemia/decreased phosphorus as an ADR, more patients treated with FCM reported occurrence of headache (4.3% vs. 3.2% for FDI) and nausea (6.8% vs. 0.8% for FDI).

Summary of evidence

Introduction: There are currently 6 FDA-approved IV iron products. All approved agents are iron-carbohydrate complexes or colloids, but differ in the size of the iron core, identity and density of the surrounding carbohydrate, and the strength of the iron-carbohydrate complex. Other differences include FDA-approved indications, requirement for a test dose, maximum safe dose per administration, and safety profile. Despite few well-conducted, head-to-head trials, all IV iron products are deemed to be equally efficacious and efficacy is generally not a distinguishing factor among the preparations. In clinical practice, the available IV iron preparations are distinguished primarily by safety profile, the maximum single dose that can be safely administered at once, and the number of doses required to deliver a repletion dose. The majority of comparative safety information is based on retrospective reviews of spontaneously reported events or data from retrospective observational studies. Due to underreporting and the reporting bias characteristic of spontaneous reports and the possibility of confounding in observational studies, it is difficult to determine if one iron preparation has a superior safety profile based on this data alone. Additionally, because serious AEs are infrequent, most prospective studies are too small or too short to assess comparative rates of these rare events. Based on the available evidence, the only high-level conclusion is that HMWD, which was withdrawn from the market in 2014, had an inferior safety profile compared with other iron preparations. The 3 most recently approved IV iron preparations, ferumoxytol, FCM and FDI, are indicated to deliver a total repletion dose of iron in 1 or 2 administrations, in contrast to the 8 to 10 administrations recommended for other iron preparations. Except for IDA associated with chemotherapy or dialysis, a full repletion dose in 1 to 2 administrations offers improved convenience. The remainder of the summary section will provide a more in-depth review of the safety and efficacy of ferumoxytol, FCM, and FDI.

Ferumoxytol: The FDA approved ferumoxytol for the treatment of IDA in adult patients with CKD in 2009 as a 510-mg dose administered over 17 seconds.[aaa] The approval was based on data from 3 pivotal trials in which oral iron was the active comparator. Two of the trials were conducted in patients with CKD stages 1-5 and 1 trial was conducted in patients with HDD-CKD. In all 3 trials, ferumoxytol was associated with significantly greater increases in Hgb at study day 35 (ranging from 0.82 g/dL to 1.22 g/dL) compared with oral iron (for which increases ranged from 0.16 g/dL to 0.52 g/dL).[kk,ll,aaa]

Subsequent to the approval of ferumoxytol, Amag Pharmaceuticals conducted 3 additional trials. Two trials, IDA-301[mm] and IDA-302[oo] were conducted in patients with IDA regardless of the underlying cause and were submitted to support Amag's sNDA to expand ferumoxytol's indication to treatment of IDA in adult patients who are intolerant of or have an unsatisfactory response to oral iron. In the IDA-301 trial, ferumoxytol was superior to placebo and in the IDA-302 trial, ferumoxytol was noninferior to IS at a noninferiority margin of −15% for the proportion of patients with an increase in Hgb level of at least 2 g/dL at any time from baseline to week 5.[mm,oo] Ferumoxytol-treated patients experienced a greater increase, by 0.3 g/dL, in mean Hgb level over 5 weeks compared with IS-treated patients, a difference that was statistically significant but likely not clinically meaningful, as quality-of-life assessments did not differ between groups.[oo] In a small phase 2 trial conducted in patients with IDA and CKD (stages 2-5), ferumoxytol was noninferior to IS at a noninferiority margin of −0.5 g/dL for the mean increase in Hgb level over 5 weeks.[pp] In both studies that used IS as the control drug, ferumoxytol treatment was associated with a shorter median time to achieve the study-defined Hgb goal; the difference was likely attributable to the difference between treatment arms in the number of doses required to administer a repletion dose of iron. Iron sucrose–treated patients had a higher incidence of AEs of special interest, defined as a composite of moderate-to-severe hypotension and moderate-to-severe HSRs.[oo,pp] In the IDA-302 trial, the rates of occurrence of the individual components of the composite endpoint were not provided.[oo] In the phase 2 trial, the difference between treatment arms was driven by a higher incidence of hypotensive events in the IS group, which is not an unexpected result given that the IS iron-carbohydrate complex releases more labile iron than ferumoxytol's complex after administration. While no patients treated with IS experienced an HSR, 1 patient (1.3%) treated with ferumoxytol experienced an event that required medical intervention.[pp]

In its initial clinical development program, ferumoxytol was well tolerated. Serious HSRs and other AEs potentially associated with hypersensitivity were reported in 0.2% (3/1,726) and 3.7% (63/1,726) of ferumoxytol-treated patients, respectively.[aaa] All pivotal trials excluded patients with multiple drug allergies or a previous hypersensitivity to IV iron, which likely caused the safety of ferumoxytol to be overestimated. Due to spontaneous reports of HSRs with ferumoxytol in clinical practice, the FDA queried its Adverse Event Reporting System database and identified 79 cases of anaphylactic reactions associated with ferumoxytol administration between June 30, 2009, and June 30, 2014. A large proportion (43%, 34/79) of the patients had a medical history of drug allergy and 24% had a history of multiple drug allergies. In March 2015, the FDA modified the prescribing information of ferumoxytol to include a boxed warning about the occurrence of HSRs, a new contraindication regarding use in patients with a history of allergic reaction to any IV iron product, and modification of the dosage and administration of ferumoxytol to require administration as a diluted infusion over 15 minutes.[bbb] While the underlying mechanism of anaphylaxis remains uncertain, not just for ferumoxytol but for all IV iron products, there is a growing consensus that the majority of HSRs to iron are not IgE-mediated. Proposed alternative mechanisms are induction of oxidative stress by release of free reactive iron and complement activation–related pseudoallergy (CARPA). Emerging research suggests that development of CARPA is infusion-rate dependent and that a slower infusion rate may lower the reactogenic potential if complement activation is a major pathogenic factor for the development of HSR.[ccc]

In February 2018, the FDA approved Amag's sNDA to expand ferumoxytol's indication to include all adult IDA patients who cannot tolerate oral iron treatment or in whom such treatment has failed. The sNDA, originally submitted to the FDA in 2012, was based on data from the IDA-301 and IDA-302 trials.[mm,oo] In 2014, the FDA issued a complete response letter that requested that Amag collect additional safety information in the IDA population and evaluate alternative dosage or administration schedules for ferumoxytol. The recently published IDA-304 trial was conducted to meet the FDA's requests.[qq] Data from this trial in addition to IDA-301 and IDA-302 support the recent approval. The IDA-304 trial was a comparison between ferumoxytol and FCM in patients with IDA and a history of unsatisfactory response to or intolerance of oral iron. To blind the study, FCM was selected as the comparator because it is approved to deliver a full repletion dose in 2 administrations. While blinding is a strength, FCM's safety profile is not as established as those of other marketed iron preparations, making it a somewhat dubious comparator for a safety trial. As opposed to previous trials in which ferumoxytol was administered as a 17-second IV push, in IDA-304 it was administrated as an IV infusion over a minimum of 15 minutes. Ferumoxytol was noninferior to FCM at a noninferiority margin of 2.6% for the adjudicated composite endpoint of moderate-to-severe HSRs (including anaphylaxis) and moderate-to-severe hypotension from baseline to week 5. The occurrence of the primary endpoint was low and similar between groups (ferumoxytol 0.6%; FCM 0.7%), but it was far below the predicted rate of 3.3% used in the sample size calculation.[qq] Therefore, the study was likely underpowered to detect a difference between ferumoxytol and FCM for relatively rare safety events in a cohort without a history of multiple drug allergies. It has been estimated that a comparative iron study would need to evaluate approximately 6,600 patients to have sufficient statistical power to detect a difference in HSRs if a difference existed.[ccc]

Ferumoxytol was also noninferior to FCM for the composite incidence of moderate-to-severe HSRs (including anaphylaxis), serious CV events, and death from baseline to week 5. More FCM-treated patients experienced a serious CV event and 23% of these events were judged to be related to treatment. In other comparative studies, FCM treatment has been associated with a higher incidence of hypertensive events. Ferumoxytol was noninferior to FCM for the mean change in Hgb from baseline to week 5 despite FCM delivering approximately a 32% higher dose of elemental iron. In an analysis that evaluated mean change in Hgb per gram of iron to account for the disparity in iron dose, ferumoxytol was superior to FCM. As noted in other trials, FCM was associated with a significantly higher incidence of hypophosphatemia (38.7% vs. 0.4% for ferumoxytol).[qq]

Ferric carboxymaltose: Ferric carboxymaltose is approved for treatment of IDA in patients who do not tolerate oral therapy or in whom it is not effective and in patients with NDD-CKD. Prior to the 2013 approval, the FDA issued 2 nonapprovable letters due to safety concerns. After the second nonapprovable letter was issued, 2 additional phase 3 trials were conducted that included a cardiac composite safety endpoint and also evaluated lower single and cumulative doses of FCM. One trial compared FCM with IS in NDD-CKD patients; the other trial compared FCM with oral iron in patients with IDA of various etiologies. Compared with oral iron and IS, FCM was associated with significantly greater increases in mean Hgb level, ferritin, transferrin saturation, and serum iron over the 5- to 8-week follow-up periods.[rr,ss] The better efficacy of FCM in trials was likely attributable to the 33% higher cumulative dose of elemental iron delivered with FCM. In both trials, the cardiac composite safety endpoint did not differ significantly between FCM and active comparators over the 4 months the endpoint was assessed,[rr,ss] though the incidence of protocol-defined hypertensive events was greater with FCM than IS.[rr] Treatment-emergent adverse events occurring more frequently with FCM versus comparators included nausea, flushing, dizziness, dysgeusia, and clinically relevant hypophosphatemia. Mild-to-moderate HSRs occurred in less than 1% of FCM-treated patients.[rr,ss] The cumulative evidence base for FCM is relatively large for a newly approved drug due to its multiple FDA submissions. In addition to the 2 pivotal trials summarized above, phase 3 trials have evaluated FCM for IDA associated with HUB, postpartum, IBD, CHF, and HDD-CKD.[m-q,tt,uu] Most of these earlier trials evaluated a dose of 1,000 mg per administration rather than 2 doses of 750 mg.

Ferric derisomaltose (iron isomaltoside): Ferric derisomaltose is approved for treatment of IDA in patients who do not tolerate oral therapy or in whom it is not effective and in patients with NDD-CKD. The product consists of iron and a carbohydrate moiety where the iron is tightly bound in a matrix structure. It has a low immunogenic potential, a low potential to release labile iron (<1% of the iron dose administered) and does not appear to cause clinically significant hypophosphatemia. Due to the structure of FDI, it can be administered in high doses (eg, 1,000 mg) with a maximum single dose of 20 mg/kg body weight.

The FERWON program was initiated to address the safety and efficacy of FDI in patients with IDA of either various etiologies (FERWON-IDA)pp or NDD-CKD (FERWON-NEPHRO).[vv,ww] Between the 2 trials, a total of 3,050 patients were randomized in a 2:1 fashion to treatment with FDI (1,000 mg single dose) or IS (single 200 mg IV injections repeated up to 5 times for a cumulative dose of 1,000 mg). While FDI induced a more rapid hematological response than IS between weeks 1 and 4, FDI was noninferior to IS for the primary efficacy endpoint, change in Hgb from baseline to week 8. Both trials, powered to rule out a ≥3% occurrence of adjudicated serious or severe HSRs in the FDI group, demonstrated that the occurrence of serious or severe HSRs was low and similar between iron groups.[vv,ww] Of note, both trials included patients with non-iron drug allergies. The prespecified pooled safety analysis of the FERWON trials was adequately powered to demonstrate that FDI was noninferior to IS for the occurrence of serious or severe HSRs based on a noninferior margin of 1.5% for the upper bound of the 95% CI for the between group risk difference.[yy] In the 6-month FERWON-EXT trial, re-dosing with FDI was not associated with an increased risk of serious or severe HSRs.[xx] In the FERWON-IDA and -NEPHRO trials, the occurrence of adjudicated composite CV events was numerically lower in the FDI treatment arm; the difference reached statistical significance in the FERWON-NEPHRO trial and in the prespecified pooled safety analysis.[vv,ww,yy] The most common CV events, all of which occurred more frequently in the IS treatment arm, were hypertension, CHF, and AF. Trials were only 8 weeks in duration; therefore, it may be difficult to attribute the effect to iron alone. Investigators noted that it is plausible that CV events were significantly lower in the FDI treatment arm because of more rapid iron repletion and less free labile iron; however, it is unclear if treatment arms were well matched for CV risk factors outside a history of CHF, MI, and stroke at baseline. IRONMAN, a large trial designed to evaluate reduction of death or worsening HF with FDI (NCT02642562) is in progress and will determine if FDI improves CV outcomes.

The occurrence of hypophosphatemia, previously associated with FCM administration, was evaluated in the FERWON trials as an adverse event and in the PHOSPHARE trials as a primary endpoint. In the FERWON trials, the incidence of hypophosphatemia (serum phosphate < 2.0 mg/dL) was low and similar between the FDI and IS treatment arms. There were no occurrences of severe hypophosphatemia (serum phosphate <1.0 mg/dL) reported in either treatment arm.[yy] In the 6-month follow-up period after FDI re-dosing, hypophosphatemia was reported in 8 patients (7.8%), of which 7 patients' hypophosphatemia was not clinically significant.[xx] In the PHOSPHARE trials, the incidence of hypophosphatemia was significantly lower with FDI vs. FCM treatment.[yy]

The comparative safety of FDI versus other iron formulations remains largely unknown. Although results from a single study that used 3 different statistical approaches to indirectly compare the risk of experiencing a serious or severe HSR with FDI, IS, and FCM suggested that FDI was associated with a 59% and 49% lower risk of experiencing a HSR relative to FCM and IS, respectively,[ddd] the FERWON trials, a direct comparison, suggested the risk of a serious or severe HSR was low and not statistically different between FDI and IS.[yy] Reported only descriptively in the PHOSPHARE trials, the frequency of adjudicated serious or severe HSRs with FDI was numerically lower than the frequency reported with FCM (0.8% vs. 1.7%). Results from a recent retrospective pharmacoepidemiologic study suggest that FDI is associated with a higher reporting rate of severe HSRs than FCM in European countries relative to estimated exposure.[eee] Due to limitations associated with indirect comparisons and pharmacovigilance studies, it is unknown if FDI is associated with fewer HSRs than IS or FCM.

An additional smaller clinical trial[fff] and observational studies[ggg] of FDI show that it is an effective and well-tolerated treatment of anemia across different therapeutic areas and maintains a favorable safety profile.

Conclusion: The choice among IV iron preparations is likely based on perceived differences in safety profiles, patient populations treated, convenience factors, and cost. All IV iron products have the potential to cause serious HSRs; whether one of the newer IV iron preparations has a superior safety profile has yet to be demonstrated in a well-designed study. Although the IV iron preparations have different FDA-approved indications, they are commonly used off-label. Efficacy is generally not a consideration; however, FCM, which delivers approximately a 33% higher dose of elemental iron than other preparations when given as 2 doses of 750 mg, is associated with greater improvements in iron indices. The main advantage of the 3 newest IV iron preparations, FDI, ferumoxytol and FCM, is that a repletion dose can be given in 1 or 2 administrations. In comparative studies with IS, administration of a full repletion dose over a shorter time period with FDI and ferumoxytol resulted in earlier achievement of Hgb goals. While LMWD can be administered off-label as a TDI, it must be infused over a minimum of 1 to 4 hours and there are lingering concerns about

its comparative safety and tolerability. Increased convenience may be important in the outpatient setting where multiple visits can contribute to overall costs. Additional evidence is required to determine if modifying ferumoxytol administration has mitigated the higher—although still rare—incidence of HSRs in patients with multiple drug allergies. Similarly, the clinical meaningfulness of hypophosphatemia with FCM requires additional study.

Abbreviations: AE = adverse event; AF = atrial fibrillation; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; D5W = 5% dextrose in water; ED = emergency department; ESA = erythropoiesis-stimulating agents; FCM = ferric carboxymaltose; FDA = Food and Drug Administration; FDI = ferric derisomaltose; HDD-CKD = hemodialysis-dependent chronic kidney disease; Hgb = hemoglobin; HMWD = high-molecular-weight iron dextran; HR = hazard ratio; HSR = hypersensitivity reactions; HUB = heavy uterine bleeding; IBD = inflammatory bowel disease; ICD-9 = International Classification of Diseases, 9th Revision; IDA = iron deficiency anemia; IgE = immunoglobulin E; IM = intramuscular; IS = iron sucrose; IV = intravenous; LMWD = low-molecular-weight iron dextran; LOE = loss of exclusivity; MRI = magnetic resonance imaging; NDD-CKD = non–dialysis-dependent chronic kidney disease; NS = normal saline; OR = odds ratio; PDD-CKD = peritoneal dialysis–dependent chronic kidney disease; SAE = serious adverse event; SFG = sodium ferric gluconate; sNDA = supplemental new drug application; SOC = standard of care; TEAE = treatment-emergent adverse event; TDI = total dose infusion.

References

a. INFeD. Package insert. Madison, NJ: Allergan USA; 2021.

b. Ferrlecit. Package insert. Bridgewater, NJ: Sanofi-Aventis; 2022.

c. Venofer. Package insert. Shirley, NY: American Regent; 2021.

d. Feraheme. Package insert. Waltham, MA: AMAG Pharmaceuticals; 2022.

e. Injecatfer. Package insert. Shirley, NY: American Regent; 2022.

f. MonoFerric. Package insert. Hoelbaek, Denmark: Pharmacosmos; 2022.

g. IPD Analytics, Payer & Provider Insights, Aventura, FL: IPD Analytics, LLC; 2022. https://www.ipdanalytics.com/. Accessed June 27, 2022.

h. Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. *Am J Hematol.* 2016;91(1):31-38.

i. Folkert VW, Michael B, Agarwal R, et al; Ferriecit Publication Committee. Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher-dose (≥ 250 mg) administration. *Am J Kidney Dis.* 2003;41(3):651-657.

j. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis*. 2001;38(5):988-991.

k. Venofer [package insert]. Shirley, NY: American Regent, Inc; 2015.

l. Auerbach M, Strauss W, Auerbach S, Rineer S, Bahrain H. Safety and efficacy of total dose infusion of 1,020 mg of ferumoxytol administered over 15 min. *Am J Hematol.* 2013;88(11):944-947.

m. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol.* 2008;103(5):1182-1192.

n. Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. *Int J Gynaecol Obstet.* 2008;101(1):67-73.

o. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion.* 2009;49(12):2719-2728.

p. Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anemia of non-dialysis-dependent chronic kidney disease patients. *Nephrol Dial Transplant.* 2011;26(5):1599-1607.

q. Charytan C, Bernardo MV, Koch TA, Butcher A, Morris D, Bregman DM. Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: a randomized, active-controlled, multicenter study. *Nephrol Dial Tranplant.* 2013;28(4):953-964.

r. Rostoker G, Cohen Y. Magnetic resonance imaging repercussions of intravenous iron products used for iron-deficiency anemia and dialysis-associated anemia. *J Comput Assist Tomogr*. 2014 Nov-Dec;38(6):843-4.

s. IPD Analytics, Access Hub, Aventura, FL: IPD Analytics, LLC; 2022. https://www.ipdanalytics.com/. Accessed June 27, 2022.

t. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. *Am J Kidney Dis*. 1999;33(3):464-470.

u. McCarthy JT, Regnier CE, Loebertmann CL, Bergstralh EJ. Adverse events in chronic hemodialysis patients receiving intravenous iron dextran — a comparison of two products. *Am J Nephrol.* 2000;20(6):455-462.

v. Fletes R, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis.* 2001;37(4):743-749.

w. Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM. A randomized, controlled parallel-group trial on efficacy and safety of iron sucrose (Venofer) vs iron gluconate (Ferrlecit) in haemodialysis patients treated with rHuEpo. *Nephrol Dial Transplant*. 2001;16(6):1239-1244.

x. Michael B, Coyne DW, Fishbane S, et al; Ferrlecit Publication Committee. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int*. 2002;61(5):1830-1839.

y. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant.* 2004;19(6):1571-1575.

z. Sheashaa H, El-Husseini A, Sabry A, et al. Parenteral iron therapy in treatment of anemia in end-stage renal disease patients: a comparative study between iron saccharate and gluconate. *Nephron Clin Pract.* 2005;99(4):c97-101.

aa. Bailie GR, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant*. 2005;20(7):1443-1449.

bb. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21(2):378-382.

cc. Sav T, Tokgoz B, Sipahioglu MH, et al. Is there a difference between the allergic potencies of the iron sucrose and low molecular weight iron dextran. *Ren Fail*. 2007;29(4):423-426.

dd. Moniem KA, Bhandari S. Tolerability and efficacy of parenteral iron therapy in hemodialysis patients, a comparison of preparations. *Transfusion Altern Transfusion Med*. 2007;9(1):37-42.

ee. Anirban G, Kohli HS, Jha V, Gupta KL, Sakhuja V. The comparative safety of various intravenous iron preparations in chronic kidney disease patients. *Ren Fail.* 2008;30(6):629-638.

ff. Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm.* 2012;69(4):310-320.

gg. Okam MM, Mandell E, Hevelone N, Wentz R, Ross A, Abel GA. Comparative rates of adverse events with different formulations of intravenous iron. *Am J Hematol.* 2012;87(11):E123-124.

hh. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA.* 2015;314(19):2062-2068.

ii. Airy M, Mandayam S, Mitani AA, et al. Comparative outcomes of predominant facility-level use of ferumoxytol versus other intravenous iron formulations in incident hemodialysis patients. *Nephrol Dial Transplant.* 2015;30(12):2068-2075.

jj. Wetmore JB, Weinhandl ED, Zhou J, Gilbertson DT. Relative incidence of acute adverse events with ferumoxytol compared to other intravenous iron compounds: a matched cohort study. *PLoS One*. 2017;12(1):e0171098. doi:10.1371/journal.pone.0171098.

kk. Spinowitz BS, Kausz AT, Baptista J, et al. Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol*. 2008;19(8):1599-1605.

ll. Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, Pereira BJ. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clin J Am Soc Nephrol.* 2009;4(2):386-393.

mm. Vadhan-Raj S, Strauss W, Ford D, e al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. *Am J Hematol.* 2014;89(1):7-12.

nn. Vadhan-Raj S, Ford DC, Dahl NV, et al. Safety and efficacy of ferumoxytol for the episodic treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy: results of a phase III, open-label, 6-month extension study. *Am J Hematol*. 2016;91(2):E3-5.

oo. Hetzel D, Strauss W, Bernard K, Li Z, Urboniene A, Allen LF. A phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy. *Am J Hematol.* 2014;89(6):646-650.

pp. Macdougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol.* 2014;9(4):705-712.

qq. Adkinson NF, Strauss WE, Macdougall IC, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: a randomized trial. *Am J Hematol.* 2018;93(5):683-690.

rr. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant.* 2014;29(4):833-842.

ss. Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion.* 2014;54(2):306-315.

tt. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstet Gynecol.* 2007;110(2 Pt 1): 267-278.

uu. Evstatiev R, Marteau P, Iqbal T, et al; FERGI Study Group. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology.* 2011;141(3):846-853.

vv. Auerbach M, Henry D, Derman RJ, Achebe MM, Thomsen LL, Glaspy J. A prospective, multi-center, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. *Am J Hematol.* 2019;94(9):1007-1014.

ww. Bhandari S, Kalra PA, Berkowitz M, Belo D, Thomsen LL, Wolf M. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. *Nephrol Dial Transplant.* 2021;36(1):111-120.

xx. Achieve MM, Glaspy J, Kalra PA, Auerbach M, Thomsen LL, Bhandari S. A 6 month extension trial evaluating safety and efficacy of ferric derisomaltose in patients with iron deficiency anemia: The FERWON-EXT trial. *Am J Hematol.* 2020;95(10):E276-E279.

yy. Wolf M, Auerbach M, Kalra PA, Glaspy J, Thomsen LL, Bhandari S. Safety of ferric derisomaltose and iron sucrose in patients with iron deficiency anemia: The FERWON-IDA/NEPHRO trials. *Am J Hematol.* 2021;96(1):E11-E15.

zz. Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs. ferric carbosymaltose on hypophosphatemia in iron-deficiency anemia: Two randomized clinical trials. *JAMA.* 2020;323(5):432-443.

aaa. Lu M, Cohen MH, Rieves D, Pazdur R. FDA report: ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. *Am J Hematol*. 2010;85(5):315-319.

bbb. McCulley L, Gelperin K, Bird S, Harris S, Wang C, Waldron P. Reports to FDA of fatal anaphylaxis associated with intravenous iron products. *Am J Hematol.* 2016;91(12):E496-E497.

ccc. Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. *Br J Pharmacol.* 2015;172(21):5025-5036.

ddd. Pollock RF, Biggar P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. *Expert Rev Hematology.* 2020;13(2):187-195.

eee. Ehlken B, Nathell L, Gohlke A, Bocuk D, Toussi M, Wholfeil S. Evaluation of the reported rates of severe hypersensitivity reactions associated with ferric carboxymaltose and iron (III) isomaltoside 1000 in Europe based on data from EudraVigilance and VigiBase between 2014 and 2017. *Drug Saf.* 2019;42(3):463-471.

fff. Derman R, Roman E, Modiano MR, et al. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. *Am J Hematol*. 2017; 92(3):286-291.

ggg. Jensen G, Gøransson LG, Fernström, et al. Treatment of iron deficiency in patients with chronic kidney disease: A prospective observational study of iron isomaltoside (NIMO Scandinavia). *Clin Nephrol.* 2019; 91(4):246-253.

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