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Drug Class Literature Scan: Iron Replacement, Oral

Date of Review: October 2025

Date of Last Review: March 2014

Literature Search: 01/01/2014–06/09/2025

Current Status of PDL Class:

See **Appendix 1**.

Plain Language Summary:

- Iron deficiency anemia can be caused by loss of blood due to bleeding ulcers or heavy menstrual periods, not getting enough iron from dietary intake, during pregnancy, or in people with a chronic disease such as kidney or heart failure.
- Iron supplementation is a key treatment option for managing iron deficiency anemia. Iron supplements are available in several different forms including tablets, capsules, solution, and drops that are taken by mouth.
- Several clinical guidelines recommend using oral ferrous sulfate, gluconate, or fumarate as treatment for iron deficiency anemia.
- Ferrous sulfate tablets, ferrous sulfate oral liquid, and ferrous gluconate tablets are available on the preferred drug list for people on the Oregon Health Plan. Iron supplements that are not preferred require prior authorization from the Oregon Health Authority before they are covered.

Conclusions:

- Since the last Pharmacy and Therapeutic (P & T) Committee review, one systematic review¹ and 4 high-quality guidelines²⁻⁵ have been published.
- A 2024 Cochrane review assessed the benefits and harms of available treatments for women with postpartum iron deficiency anemia.¹ The available evidence is very low-quality as most of the trials were open-label and not blinded. Eighteen randomized controlled trials (RCTs) compared intravenous iron with oral iron in women with a postpartum hemoglobin value of 12 g/dL or less within 6 weeks after delivery.¹ Low-quality evidence shows that intravenous iron probably reduces fatigue slightly in the early postpartum weeks (8 to 28 days) compared to oral iron tablets but probably results in little to no difference after 4 weeks.¹ Iron tablets probably result in a large increase in constipation compared to intravenous iron (moderate-quality evidence).¹
- In 2019, the British Society for Hematology (BSH) issued guidance for management of iron deficiency in pregnancy.² Recommendations and strength of evidence for the use of oral iron for iron deficiency pregnancy are as follows:
 - Ferrous iron salts are the current preparation of choice for oral iron supplementation (Strong Recommendation, Moderate-Quality Evidence).²
 - Until further research determines the optimal dose of elemental oral iron, 40–80 mg every morning is suggested, checking hemoglobin at 2–3 weeks to ensure an adequate response (Weak Recommendation, Low-Quality Evidence).²
 - For nausea and epigastric discomfort, alternate day dosing or preparations with lower iron content should be tried. Slow-release and enteric-coated forms should be avoided (Strong Recommendation, High-Quality Evidence).²
- In 2021 American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin to provide recommendations for screening and clinical management of anemia during pregnancy.³ Low-dose iron supplementation is recommended starting in the first trimester to decrease the prevalence of maternal anemia at delivery (high-quality evidence).³

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- In 2021 the British Society Of Gastroenterology (BSG) issued guidance for management of iron deficiency anemia in adults.⁴ Recommendations and strength of evidence for oral iron replacement in adults with iron deficiency anemia are as follows:
 - Initial treatment of iron deficiency anemia should be with one tablet per day of ferrous sulfate, fumarate or gluconate. If not tolerated, a reduced dose of one tablet every other day, an alternative oral preparation, or parenteral iron should be considered (Strong Recommendation, Moderate-Quality Evidence).⁴
 - Parenteral iron should be considered when oral iron is contraindicated, ineffective or not tolerated. This consideration should be at any early stage if oral iron replacement therapy is judged unlikely to be effective, or the correction of anemia is particularly urgent (Strong Recommendation, High-Quality Evidence).⁴
- In 2020, the Swiss Pediatric Oncology Group (SPOG) published guidance for diagnosing and managing iron deficiency in children with or without anemia.⁵ Oral iron replacement is effective in most children with iron deficiency anemia and should be initiated when a definitive laboratory diagnosis is established.⁵
- A new prescription form of iron, ACCRUFER (ferric maltol) received Food and Drug Administration (FDA) approval in July 2019.²⁰ Ferric maltol is indicated for treatment of iron deficiency in adults.²⁰

Recommendations:

- Based on review of clinical evidence, no changes to the PDL are warranted.
- Maintain ferric maltol as nonpreferred on the PDL.
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy

- Oral iron products were discussed at the March 2014 P & T Committee meeting. Oral iron therapy remains first-line treatment for iron deficiency anemia. These include the ferrous salts, such as ferrous fumarate, ferrous sulfate, and ferrous gluconate. Due to no evidence of differences in efficacy, comparative costs were evaluated in the executive session for preferred products. After executive session, ferrous sulfate oral suspension and oral drops were designated as nonpreferred on the Preferred Drug List (PDL) and all other ferrous sulfate products were designated as preferred.
- The status of all oral iron replacement products is presented in **Appendix 1**. Ferrous sulfate tablets, ferrous sulfate liquid, and ferrous gluconate tablets are preferred. All other formulations are non-preferred and subject to prior authorization (PA) criteria for non-preferred products.
- In order for prescription drugs to be covered by Medicaid, manufacturers generally have to participate in the Medicaid rebate program. However, unlike prescription products, the state has more flexibility to cover non-rebatable over the counter (OTC) medications. Many OTC products are eligible for rebate, and while use of rebatable OTC products is encouraged, the state can make exceptions to cover non-rebatable OTCs. Products which have historically been added to the rebate exception list are generally preferred in a PDL class and have no comparable, rebatable, and marketed alternatives.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality

and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane: Treatment for Women with Postpartum Iron Deficiency Anemia

A 2024 Cochrane review assessed the benefits and harms of available treatments for women with postpartum iron deficiency anemia.¹ This publication updated a previous 2015 publication.¹ Treatments of interest for women with a postpartum hemoglobin value of 12 g/dL or less included oral iron supplementation, intravenous iron, red blood cell transfusion and erythropoietin.¹ Outcomes included maternal mortality, patient-reported fatigue, adverse events, and persistent anemia symptoms, defined as hemoglobin less than 9 g/dL at the end of treatment.¹ Literature was searched through April 2024 and 33 RCTs (n=4,558) met inclusion criteria.¹ Eighteen trials (n=3,026) compared intravenous iron with oral iron supplements, 3 RCTs (n=229) studied intravenous and oral iron supplementation versus just oral iron supplementation, and 3 RCTs (n=237) compared oral iron supplementation with placebo or no treatment.¹ The rest of the trials evaluated erythropoietin and red blood cell transfusion as treatments for iron deficiency anemia.¹ The majority of included trials had a high risk of bias in at least two domains.¹ Specifically, blinding of participants and outcome assessors was rare.¹ While this may not affect laboratory values, it could have influenced the outcome of patient-reported fatigue.¹

- **Intravenous Iron Versus Oral Iron Supplementation**

Intravenous iron was in the form of either iron carboxymaltose (6 RCTs), iron dextran (2 RCTs), iron isomaltoside (1 RCT), or iron sucrose (9 RCTs).¹ Doses differed across RCTs, with a total dose range of 300 mg to 2500 mg.¹ Oral iron supplementation was given as ferrous sulfate, typically using a fixed dose.¹ Treatment regimens differed between trials with regard to doses, number of iron tablets per day, and number of days of treatment.¹ Non-elemental iron doses ranged from 100 mg to 325 mg per tablet from one to three times a day.¹ The evidence is very uncertain about the effect of intravenous iron on mortality (relative risk [RR] 2.95, 95% confidence interval [CI] 0.12 to 71.96; P=0.51; I² = not applicable; 3 RCTs; 1 event; n=572; very low-certainty evidence). Intravenous iron probably results in a slight reduction in fatigue within 8 to 28 days (standardized mean difference [SMD] -0.25, 95% CI -0.42 to -0.07; P=0.006; I² = 47%; 2 RCTs; n=515; moderate-certainty evidence).¹ An SMD of -0.25 is usually considered a small effect.¹ Oral iron probably increases the risk of constipation compared to intravenous iron (RR 0.12, 95% CI 0.06 to 0.21; P < 0.001; I² = 0%; 10 RCTs; n=1798; moderate-certainty evidence).¹ The RCTs that reported on hemoglobin at 8 to 28 days were too heterogeneous to pool. However, 5 of 6 RCTs favored intravenous iron compared to oral iron replacement, with mean changes in hemoglobin ranging from 0.73 to 2.10 g/dL (low-certainty evidence).¹

- **Intravenous Iron and Oral Iron Supplementation Versus Oral Iron Supplementation**

One RCT administered placebo erythropoietin in the intervention arm, and another RCT administered placebo intravenous iron in the comparator arm resulting in the comparison of intravenous and oral iron supplementation versus oral iron supplementation.¹ In the third RCT, Group A received intravenous iron immediately after giving birth and started iron tablet therapy after four weeks, while Group B received oral iron supplementation immediately after delivery.¹ Maternal mortality was not reported in any of the RCTs. Only one RCT (n=128) evaluated fatigue and reported a greater improvement in fatigue in the intravenous and oral iron group, compared to those who received only oral iron supplementation, but the effect size could not be calculated (very low-certainty evidence).¹ Intravenous iron and oral iron may result in a reduction in constipation compared to oral iron alone (RR 0.21, 95% CI 0.07 to 0.69; P=0.01; 1 RCT;

n=128; low-certainty evidence).¹ Intravenous iron and oral iron may result in little to no difference in hemoglobin at 8 to 28 days (MD 0.00, 95% CI -0.48 to 0.48; P=1.00; 1 RCT; n=60; low-certainty evidence).¹

- Oral Iron Supplementation Versus Placebo or No Treatment

Three RCTs compared oral iron supplementation with placebo. However, the trials reported on different outcomes and a meta-analysis for this comparison could not be completed.¹ A study from 1972 reported on hemoglobin values within one week post-intervention/postpartum and suggested oral iron supplementation probably increases hemoglobin within 0 to 7 days slightly (mean difference [MD] 1.01, 95% CI 0.36 to 1.66; P=0.002; 1 RCT; n=64; moderate-certainty evidence).¹ No trials reported hemoglobin values within 8 to 28 days post-intervention/postpartum.¹ All 3 trials reported hemoglobin values after 28 days postpartum.¹ The trials were too heterogeneous to combine (3 RCTs; n=237) and an insufficient number of studies precluded heterogeneity examination and subgrouping.¹ However, all 3 trials showed a benefit of oral iron supplementation, with mean increases in hemoglobin ranging from 0.60 to 2.47 g/dL.¹

In summary, the available evidence to evaluate treatment of iron deficiency in post-partum women is very low quality as most of the trials were open-label and not blinded.¹ Low-quality evidence shows intravenous iron probably reduces fatigue slightly in the early postpartum weeks (8 to 28 days) compared to oral iron tablets but probably results in little to no difference after 4 weeks.¹ Intravenous iron may increase hemoglobin slightly more than iron tablets, but the data were too heterogeneous to pool.¹ Moderate-quality evidence shows oral iron tablets probably result in increased constipation compared to intravenous iron.¹

After review, 10 systematic reviews were excluded due to poor quality or network meta-analysis,⁶ wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),⁷⁻¹⁵ or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

British Society for Hematology: Management of Iron Deficiency in Pregnancy

In 2019, the BSH issued guidance for management of iron deficiency in pregnancy.² The prevalence of maternal anemia approaches 50% in low- and middle-income countries, largely due to a combination of nutritional deficiency, infectious diseases and the presence of a variant hemoglobin or a thalassemic disorder.² Iron is an essential requirement for erythropoiesis and iron-dependent enzymes are present in all cells, including placental and fetal tissue.² Iron deficiency anemia has been linked to poor health outcomes in the mother, fetus and infant.²

Ferrous salts are preferred oral formulations to ferric salts due to the poorer absorption and bioavailability of ferric salts.² Available oral ferrous salts include ferrous fumarate, ferrous sulfate and ferrous gluconate. The amount of elemental iron is important and varies by preparation, as presented in **Table 1**. Multivitamins and OTC preparations have insufficient iron to correct anemia and often contain other minerals that interfere with iron absorption.² Combined iron and folic acid preparations are available but their efficacy compared to oral iron alone is unknown.²

Table 1. Elemental Content of Oral Iron Preparations²

Iron Salt	Preparation	Elemental Iron Content
Ferrous fumarate	210 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous sulfate	200 mg	65 mg

The recommended dose of elemental iron for treatment of iron deficiency has been 100–200 mg daily.² However, more recent studies suggest that lower doses or intermittent supplementation may be advantageous.² Studies have shown that fractional absorption of iron in iron-depleted young non-pregnant women is maximized by taking elemental iron doses of 40–80 mg once per day or alternate days, avoiding twice daily dosing.² Higher doses potentially increase side effects due to the excess unabsorbed iron remaining in the gastrointestinal (GI) tract.² Iron can cause gastric irritation, nausea and disturbed bowel function, affecting adherence.² Data suggests that optimal absorption occurs from alternate day dosing.² However, a balance between optimal absorption, ease of compliance and need for rapid response lead to preference for a daily regimen.² Oral iron supplementation should be taken on an empty stomach, as absorption is reduced or promoted by the same factors that affect absorption of dietary non-heme iron.² Oral iron supplements may be taken with water or a source of vitamin C to enhance absorption.²

Iron salts may cause gastric irritation and up to one third of patients may develop dose-limiting side effects including nausea and epigastric discomfort.² This is minimized by correct administration, which optimizes absorption.² It may be necessary to titrate the dose down to a level where side effects are acceptable or try an alternative preparation.² Enteric-coated or sustained release preparations should be avoided, as the majority of the iron from such preparations is carried past the duodenum, limiting absorption.² Recommendations and strength of evidence for the use of oral iron for iron deficiency pregnancy are as follows:

- Once women become iron-deficient in pregnancy it is not possible to ensure repletion through diet alone and oral supplementation is needed (Fair Recommendation, Moderate-Quality Evidence).²
- Ferrous iron salts are the current preparation of choice for oral iron supplementation (Strong Recommendation, Moderate-Quality Evidence).²
- Until further research determines the optimal dose of elemental oral iron, 40–80 mg every morning is suggested, checking hemoglobin at 2–3 weeks to ensure adequate response (Weak Recommendation, Low-Quality Evidence).²
- For nausea and epigastric discomfort, alternate day dosing or preparations with lower iron content should be tried. Slow-release and enteric-coated forms should be avoided (Strong Recommendation, High-Quality Evidence).²
- Women with hemoglobin less than 100 g/L within 48 hours of delivery, who are hemodynamically stable, asymptomatic, or mildly symptomatic, should be offered oral elemental iron 40–80 mg daily for at least 3 months (Fair Recommendation, High-Quality Evidence).²
- There is insufficient evidence to assess the benefits and potential hazards of routine iron supplementation for all women in pregnancy (Fair Recommendation, Low-Quality Evidence).²

American College of Obstetricians and Gynecologists: Anemia in Pregnancy

In 2021 ACOG issued a practice bulletin to provide recommendations for screening and clinical management of anemia during pregnancy.³ All pregnant women should be screened for anemia with a complete blood count in the first trimester and again at 24 to 28 weeks of gestation.³ Patients who meet criteria for anemia based on hematocrit levels less than 33% in the first and third trimesters and less than 32% in the second trimester should be evaluated to determine the cause.³ If iron deficiency is ruled out, other etiologies should be investigated.³ Iron deficiency anemia during pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality and should be treated with iron supplementation in addition to prenatal vitamins.³ The ACOG issued one recommendation for use of oral iron replacement therapy to manage anemia in pregnancy:

- Low-dose iron supplementation is recommended starting in the first trimester to decrease the prevalence of maternal anemia at delivery (high-quality evidence).³

British Society of Gastroenterology Guidelines for The Management of Iron Deficiency Anemia in Adults

In 2021, the BSG issued guidance for management of iron deficiency anemia in adults.⁴ Iron deficiency anemia is a major cause of morbidity and burden of disease worldwide.⁴ It can generally be diagnosed by blood testing and managed by iron replacement therapy using oral or intravenous formulations.⁴ The causes of iron deficiency include poor dietary intake and malabsorption of dietary iron, as well as a number of significant GI pathologies.⁴ Because blood is iron-rich it can result from chronic blood loss, and this is a common mechanism underlying the development of iron deficiency anemia, for example, as a consequence of menstrual or GI blood loss.⁴ Iron deficiency anemia is also associated with the anemia of chronic diseases including heart failure, kidney disease, rheumatoid arthritis, and inflammatory bowel disease.⁴

Traditional oral iron salts (ferrous sulfate, ferrous gluconate and ferrous fumarate) are effective, safe, and readily available, and they are the standard therapies for iron deficiency anemia.⁴ Their use is supported by considerable clinical experience and observational data.⁴ In a pooled analysis of trial data, 72.8% of patients with iron deficiency anemia demonstrated a satisfactory response to an oral iron formulation, defined as an hemoglobin increase of at least 10 g/L within 2 weeks, though rates of normalization of hemoglobin were lower with continued bleeding or clinically evident GI disease.¹⁶ A 2014 Cochrane analysis noted that the trials were of poor quality, but concluded that in comparison to placebo, oral iron replacement therapy significantly improves hemoglobin levels in iron deficiency anemia and probably reduces blood transfusion requirements.¹⁷ Modified-release preparations release iron in the more distal small bowel beyond the areas of most active assimilation and they do not enhance iron absorption or reduce side effects; therefore, their use is not recommended.⁴

Intermittent oral iron (defined as less frequently than daily) has been reported to be at least as effective as daily dosing in raising hemoglobin levels in young women and during pregnancy, although less effective in boosting iron stores in the short-term.⁴ Intermittent oral iron is associated with a lower incidence of GI adverse events in pregnant women (RR 0.56; 95% CI 0.37 to 0.84).⁴ The optimal drug, dosage and timing of oral iron replacement therapy for adults with iron deficiency anemia are not clearly defined, and the effect of alternate day therapy on adherence and ultimate hematological response are unclear.⁴ Based on the available literature, a once daily dose of 50–100 mg of elemental iron (e.g., one ferrous sulfate 200 mg tablet a day) taken in the fasting state may be the best option for initial treatment.⁴ Whatever agent and regimen are selected, it is essential to monitor the initial hematological response and modify as appropriate with apparent therapeutic failure.⁴ Recommendations and strength of evidence for oral iron replacement in adults with iron deficiency anemia are as follows:

- Initial treatment of iron deficiency anemia should be with one tablet per day using ferrous sulfate, fumarate or gluconate formulations. If not tolerated, a reduced dose every other day, alternative oral preparations or parenteral iron should be considered (Strong Recommendation, Moderate-Quality Evidence).⁴
- Patients should be monitored in the first 4 weeks for a hemoglobin response to oral iron, and treatment should be continued for about 3 months after normalization of the hemoglobin level to ensure adequate repletion of the marrow iron stores (Strong Recommendation, Moderate-Quality Evidence).⁴
- Parenteral iron should be considered when oral iron is contraindicated, ineffective or not tolerated. This consideration should be at any early stage if oral iron replacement therapy is judged unlikely to be effective or if the correction of anemia is particularly urgent (Strong Recommendation, High-Quality Evidence).⁴

Swiss Pediatric Oncology Group: Diagnosis and Management of Iron Deficiency in Children with or Without Anemia

In 2020, the SPOG Pediatric Hematology Working Group published guidance for managing iron deficiency in children (aged 0 to 18 years old) with or without anemia.⁵ Iron plays a crucial role in the cognitive development of children and adolescents.⁵ In children, iron deficiency can lead to delayed cognitive, motor, attention and memory deficits, visual and auditory deficits, decreased school performance, or behavioral disorders, some with persistent long-term effects.⁵ Oral iron substitution is effective in most children with iron deficiency anemia and should be initiated when a clear laboratory diagnosis is established.⁵ Side effects can occur but are rarely dangerous. Detailed education and information of the family regarding possible side effects (constipation, some upper GI-irritation initially, tainting of teeth) at the beginning of therapy is strongly recommended, as it will help to improve adherence.⁵

The recommended duration of oral iron substitution is 2–3 months.⁵ Monitoring therapy response is only necessary in cases with severe anemia or continuous iron losses (i.e., menorrhagia) or in case of suspected poor/insufficient adherence.⁵

After review, 2 guidelines were excluded due to poor quality.^{18,19}

New Formulations:

A new prescription form of iron, ACCRUFER (ferric maltol) received FDA approval in July 2019.²⁰ Ferric maltol is indicated for treatment of iron deficiency in adults.²⁰ The dose is one 30 mg capsule taken twice daily on an empty stomach.²⁰ The safety and efficacy of ferric maltol for treatment of iron deficiency anemia was studied in 3 placebo-controlled RCTs.²⁰ Adults with quiescent irritable bowel disease (IBD) and baseline hemoglobin concentrations between 9.5 g/dL and 12/13 g/dL for males/females, and ferritin > 30 mcg/L met inclusion criteria for 2 RCTs.²⁰ Forty-five males and 83 females were enrolled in these 2 RCTs. All patients had discontinued prior oral iron supplementation due to lack of efficacy or inability to tolerate oral iron replacement products.²⁰ Patients were randomized 1:1 to receive either 30 mg ferric maltol twice daily or a matched placebo control for 12 weeks.²⁰ The primary efficacy outcome was mean difference in hemoglobin concentration from baseline to week 12.²⁰ At 12 weeks, the ferric maltol-treated patients had a least square mean (LSM) improvement in hemoglobin of 2.25 g/dL compared with placebo-treated patients, who had a 0.06 LSM change in hemoglobin concentration (LSM difference = 2.18 g/dL; $p < 0.0001$).²⁰

The safety and efficacy of ferric maltol for the treatment of iron deficiency anemia was also studied in a trial that enrolled 167 patients with non-dialysis dependent chronic kidney disease and baseline hemoglobin concentrations between 8g/dL and 11 g/dL and ferritin < 250 mcg/L with a Transferrin saturation (TSAT) <25% or ferritin < 500 mcg/L with a TSAT <15%.²⁰ The mean age of enrolled patients was 67.4 years, consisting of 50 males and 117 females.²⁰ Subjects were randomized 2:1 to receive either 30 mg ferric maltol twice daily or a matched placebo control for 16 weeks.²⁰ The primary outcome was the mean difference in hemoglobin concentration from baseline to week 16 between ferric maltol and placebo. At 16 weeks the ferric maltol-treated patients had a LSM improved hemoglobin of 0.05 g/dL versus a -0.02 g/dL hemoglobin change in placebo-treated patients.²⁰ The LSM mean difference from baseline was 0.52 g/dL (95% CI, 0.10 to 0.93; $p = 0.0149$).²⁰

The most common adverse reaction leading to discontinuation of ferric maltol in these studies was abdominal pain (1.7% of patients).²⁰ The most frequently reported adverse events in ferric maltol-treated patients included flatulence (4.6%), diarrhea (4%), constipation (4%), discolored feces (4%), and abdominal pain (2.9%).²⁰ Warnings and precautions issued by the manufacturer included the risk of increased IBD flare due to the risk of gastrointestinal inflammation and the possibility of iron overload.²⁰

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL	OTC*
ferrous sulfate	FERROUS SULFATE	ORAL	LIQUID	Y	Q
ferrous gluconate	FERATE	ORAL	TABLET	Y	O
ferrous sulfate	FEROSUL	ORAL	TABLET	Y	Q
ferrous sulfate	FERRO-TIME	ORAL	TABLET	Y	Q
ferrous gluconate	FERROUS GLUCONATE	ORAL	TABLET	Y	Q
ferrous sulfate	FERROUS SULFATE	ORAL	TABLET	Y	O
ferrous sulfate	FERROUS SULFATE	ORAL	TABLET	Y	Q
ferrous sulfate	IRON	ORAL	TABLET	Y	Q
ferrous sulfate	FERROUS SULFATE	ORAL	TABLET DR	Y	O
ferrous sulfate	FERROUS SULFATE	ORAL	TABLET DR	Y	Q
ferric maltol	ACCRUFER	ORAL	CAPSULE	N	F
mv-mins no.73/iron fum/folic	CENTRATEX	ORAL	CAPSULE	N	F
iron/C/folate 6/B12/Zn/stomach	CHROMAGEN	ORAL	CAPSULE	N	F
iron/C/folate/B12/biot/cupric	FERIVA FA	ORAL	CAPSULE	N	F
iron fum,ps/folic acid/vitC/B3	FOLIVANE-F	ORAL	CAPSULE	N	F
iron fum,ps/folic/Bcomp,C no.9	IRON FOLATE PLUS	ORAL	CAPSULE	N	Q
iron fum,ps/folic acid/vitC/B3	IRON FOLATE-F	ORAL	CAPSULE	N	Q
iron polysaccharide complex	POLYSACCHARIDE IRON	ORAL	CAPSULE	N	Q
iron bg,ps/vitC/B12/FA/calcium	TARON FORTE	ORAL	CAPSULE	N	F
iron fumarate/vit C/Vit B12/FA	TRIGELS-F FORTE	ORAL	CAPSULE	N	F
ferrous sulfate	CHILDREN'S IRON	ORAL	DROPS	N	Q
ferrous sulfate	FERROUS SULFATE	ORAL	DROPS	N	O
ferrous sulfate	FERROUS SULFATE	ORAL	DROPS	N	Q
ferrous sulfate	INFANT-TODDLER IRON	ORAL	DROPS	N	Q
ferrous sulfate	FERROUS SULFATE	ORAL	ELIXIR	N	O
ferrous sulfate	FERROUS SULFATE	ORAL	ELIXIR	N	Q
iron polysaccharide complex	HEMATEX	ORAL	LIQUID	N	Q
ferrous sulfate	FERROUS SULFATE	ORAL	SOLUTION	N	Q
ferrous fumarate	FEOSTAT	ORAL	TAB CHEW	N	O
iron,carbonyl	IRON CHEWS	ORAL	TAB CHEW	N	Q
iron,carbonyl/folic acid/mv-mn	ACTIVE FE	ORAL	TABLET	N	F
ferrous sulfate/folic acid	BENTIVITE BX	ORAL	TABLET	N	F
iron carb,gl/FA/B12/C/docusate	CITRANATAL BLOOM	ORAL	TABLET	N	F
iron/folic acid/C/B6/B12/zinc	CORVITA 150	ORAL	TABLET	N	F
iron,carb/folate6/mv,min no.41	CORVITE 150	ORAL	TABLET	N	F
iron/folate no.6/mv,mins no.40	CORVITE FE	ORAL	TABLET	N	F
ferrous gluconate	FERATE	ORAL	TABLET	N	Q
ferrous gluconate	FERGON	ORAL	TABLET	N	Q

iron/C/B12/folate/zinc/succin	FERIVA 21-7	ORAL	TABLET	N	F
iron carb,gl/FA/B12/C/docusate	FERRALET 90	ORAL	TABLET	N	F
iron/folic acid/B12/C/docusate	FERRAPLUS 90	ORAL	TABLET	N	F
ferrous fumarate	FERRIMIN 150	ORAL	TABLET	N	Q
ferrous fumarate	FERROUS FUMARATE	ORAL	TABLET	N	Q
iron bg,ps/folic/B,C no.12/suc	IROSPAN	ORAL	TABLET	N	F
iron ag,ps/C/FA6/B12/Zn/sa/sto	NIFEREX	ORAL	TABLET	N	F
iron/folate 9/vit C/D3/B6/B12	NUFERA	ORAL	TABLET	N	F
ferrous sulfate/folic acid	TULIVITE	ORAL	TABLET	N	Q
iron/calcium/E/folic acid/mvit	VITAFOL	ORAL	TABLET	N	F
ferrous sulfate/vit C/folic ac	FOLITAB 500	ORAL	TABLET ER	N	Q
ferrous sulfate, dried	IRON	ORAL	TABLET ER	N	Q
ferrous sulfate	SLOW-RELEASE IRON	ORAL	TABLET ER	N	O
ferrous sulfate/vit Bcomp,C	IBERET	ORAL	LIQUID		O
iron/vitamin B comp and C	IBERET-500	ORAL	LIQUID		O
ferrous gluconate/vit C/B12-if	FERGON PLUS	ORAL	TABLET		F
iron/C/B12/folate/zinc/succin	FERIVA 21-7	ORAL	TABLET		Q
iron	FEROSUL	ORAL	TABLET		O
ferrous sulfate	FERROUS SULFATE	ORAL	TABLET		O
iron polysaccharide complex	HEMATEX	ORAL	TABLET		Q
iron asp gly/C/B12/FA/Zn/succ	NIFEREX	ORAL	TABLET		Q
iron/FA/C/E/B12/bio/copper/dss	TL-HEM 150	ORAL	TABLET		F

***Key to OTC codes:**

F = Legend Drug

O = Over the Counter Drug

Q = Non-Drug Supplement

Appendix 2: New Comparative Clinical Trials

A total of 238 citations were manually reviewed from the initial literature search. After further review, 237 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Powers, et al. ²¹ DB, RCT	1. Ferrous Sulfate oral drops 3 mg/kg once daily Vs. 2. Iron Polysaccharide Complex oral drops 3 mg/kg once daily	1. n=28 2. n=31 Inclusion criteria: Infants aged 9 to 48 mos with nutritional IDA -Median age: 23 mos -Male: 55% -Ethnicity: Hispanic White: 61% Non-Hispanic White: 9% Black: 11% -Baseline Hgb = 7.8 g/dL	Change in Hgb over 12 weeks.	Increased in Hgb 1. 4.0 g/dL 2. 3.4 g/dL Mean difference: 0.6 g/dL; 95% CI, 0.4 to 1.6; p<0.001 Ferrous sulfate resulted in a greater increase in Hgb at 12 weeks.	-Substantial attrition (30% in ferrous sulfate arm and 22% in polysaccharide arm). Reasons for study discontinuation were not provided. -Small study population -Funded by manufacturer of polysaccharide iron complex; one investigator received a salary from the manufacturer.
Abbreviations: CI = confidence interval; DB = double blind; dL = deciliter; g = grams; Hgb = hemoglobin; IDA = iron deficiency anemia; mos = months; n = number; RCT = randomized clinical trial					

Appendix 3: Abstracts of Comparative Clinical Trials

Effect of Low-Dose Ferrous Sulfate vs Iron Polysaccharide Complex on Hemoglobin Concentration in Young Children with Nutritional Iron-Deficiency Anemia: A Randomized Clinical Trial

Objective: To compare the effect of ferrous sulfate with iron polysaccharide complex on hemoglobin concentration in infants and children with nutritional IDA.

Design, Setting, And Participants: Double-blind, superiority randomized clinical trial of infants and children aged 9 to 48 months with nutritional IDA (assessed by history and laboratory criteria) that was conducted in an outpatient hematology clinic at a US tertiary care hospital from September 2013 through November 2015; 12-week follow-up ended in January 2016.

Interventions: Three mg/kg of elemental iron once daily as either ferrous sulfate drops or iron polysaccharide complex drops for 12 weeks.

Main Outcomes and Measures: Primary outcome was change in hemoglobin over 12 weeks. Secondary outcomes included complete resolution of IDA (defined as hemoglobin concentration >11 g/dL, mean corpuscular volume >70 fL, reticulocyte hemoglobin equivalent >25 pg, serum ferritin level >15 ng/mL, and total iron-binding capacity <425 μ g/dL at the 12-week visit), changes in serum ferritin level and total iron-binding capacity, adverse effects.

Results: Of 80 randomized infants and children (median age, 22 months; 55% male; 61% Hispanic white; 40 per group), 59 completed the trial (28 [70%] in ferrous sulfate group; 31 [78%] in iron polysaccharide complex group). From baseline to 12 weeks, mean hemoglobin increased from 7.9 to 11.9 g/dL (ferrous sulfate group) vs 7.7 to 11.1 g/dL (iron complex group), a greater difference of 1.0 g/dL (95% CI, 0.4 to 1.6 g/dL; $P < .001$) with ferrous sulfate (based on a linear mixed model). Proportion with a complete resolution of IDA was higher in the ferrous sulfate group (29% vs 6%; $P = .04$). Median serum ferritin level increased from 3.0 to 15.6 ng/mL (ferrous sulfate) vs 2.0 to 7.5 ng/mL (iron complex) over 12 weeks, a greater difference of 10.2 ng/mL (95% CI, 6.2 to 14.1 ng/mL; $P < .001$) with ferrous sulfate. Mean total iron-binding capacity decreased from 501 to 389 μ g/dL (ferrous sulfate) vs 506 to 417 μ g/dL (iron complex) (a greater difference of -50 μ g/dL [95% CI, -86 to -14 μ g/dL] with ferrous sulfate; $P < .001$). There were more reports of diarrhea in the iron complex group than in the ferrous sulfate group (58% vs 35%, respectively; $P = .04$).

Conclusions And Relevance: Among infants and children aged 9 to 48 months with nutritional iron-deficiency anemia, ferrous sulfate compared with iron polysaccharide complex resulted in a greater increase in hemoglobin concentration at 12 weeks. Once daily, low-dose ferrous sulfate should be considered for children with nutritional iron-deficiency anemia. Trial registration: clinicaltrials.gov Identifier: NCT01904864.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to June 09, 2025>

1	Ferric Compounds/ or Ferrous Compounds/ or ferrous sulfate.mp.	36093
2	ferrous gluconate.mp.	166
3	ferrous fumarate.mp.	515
4	iron polysaccharide.mp.	24
5	Anemia, Iron-Deficiency/th [Therapy]	847
6	1 or 2 or 3 or 4	36371
7	limit 6 to (english language and humans and yr="2015 -Current" and (comparative study or practice guideline or "systematic review"))	238

Appendix 5: Key Inclusion Criteria

Population	Adults and children with iron deficiency anemia
Intervention	Oral iron supplementation
Comparator	Another iron formulation
Outcomes	Increased hemoglobin, resolution of anemia symptoms (fatigue)
Timing	1 to 3 months
Setting	Outpatient