Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Review

CDA-AMC Reimbursement Recommendation

(Draft)

Ferric carboxymaltose (Ferinject)

Indication: For the treatment of iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older when oral iron preparations are not tolerated or are ineffective.

Sponsor: CSL Vifor

Recommendation: Reimburse with Conditions

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Single Technology

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that ferric carboxymaltose injection be reimbursed for the treatment of iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older when oral iron preparations are not tolerated or are ineffective only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two pivotal Phase 3 open-label RCTs (VIT-IV-CL-015: N=240 and FERGIcor: N=485) and 2 additional RCTs (1VIT05006: N=559 and VIT-IRON-2011-004: N=371) demonstrated that treatment with ferric carboxymaltose resulted in a similar clinical benefit for patients with iron deficiency anemia (IDA) compared with intravenous iron sucrose in improving hemoglobin levels, ferritin, and transferrin saturation (TSAT) levels.

Patients identified improved energy, reduced fatigue, and improved quality of life as outcomes of interest for IDA therapies. Additionally, patients were interested in IDA treatments that will enhance convenience (fewer infusions), are better absorbed, and have fewer side effects. Compared to intravenous iron sucrose, CDEC concluded that ferric carboxymaltose provides a high-dose formulation requiring fewer infusions that may offer enhanced convenience and improve quality of life.

CDEC noted that the risk of hypophosphatemia was higher with ferric carboxymaltose than with iron sucrose or ferric derisomaltose. The committee discussed that patients with underlying risk factors for hypophosphatemia may require monitoring of serum phosphate if they require multiple doses of ferric carboxymaltose for long-term treatment.

At the sponsor-submitted price for ferric carboxymaltose and publicly listed prices for all other drugs, ferric carboxymaltose may incurr lower total costs compared to iron sucrose. This is primarily due to differences in infusion time and frequency which may result in reduced administration costs for ferric carboxymaltose (e.g., supplies, chair time, nursing time). However, the total costs of ferric carboxymaltose are relatively similar to those of ferric derisomaltose. Ferric carboxymaltose is not expected to consistently yield savings with respect to administration cost given that ferric derisomaltose allows for a higher maximum dose per single infusion. CDEC notes that if patients develop more severe adverse events (e.g., severe hypophosphatemia, hypophosphatemia osteomalacia and/or fractures), savings associated with the reimbursement of ferric carboxymaltose may be further reduced or eliminated, which has not been captured in the economic analysis. Due to the uncertainty associated with savings in administration costs and the comparative safety assumptions, a price reduction for ferric carboxymaltose would be required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of ferric carboxymaltose injection should be based on the criteria used by each of the public drug plans for initiation, renewal, and prescribing IV iron formulations currently reimbursed for the treatment of iron deficiency anemia.	There is no evidence that ferric carboxymaltose injection should be held to a different standard than other IV iron formulations currently reimbursed when considering initiation, renewal, and prescribing. The clinical expert noted that the place in therapy for ferric carboxymaltose injection is comparable to other IV iron formulations, and the drug presents a high-dose option requiring fewer infusions when compared to the currently used off-label iron sucrose in pregnant patients.	CDEC agreed with the clinical experts' advice that the minimum duration of follow-up to assess the efficacy of iron supplementation treatment with ferric carboxymaltose injection would be 4 weeks, with 12 weeks as ideal.
Renewal		
2. Renewal of reimbursement for ferric carboxymaltose injection should be based on the eligibility criteria used by each public drug program to reimburse other IV iron formulations.	There is no evidence that ferric carboxymaltose injection should be held to a standard different from other IV iron formulations when considering renewal.	—
Discontinuation		
3. Discontinuation of ferric carboxymaltose injection reimbursement should be based on the eligibility criteria used by each public drug program to reimburse other IV iron formulations.	There is no evidence that ferric carboxymaltose injection should be held to a standard different from other IV iron formulations when considering renewal.	—
Prescribing		
4. Ferric carboxymaltose injection should be prescribed by clinicians with expertise in managing iron deficiency anemia in adult and pediatric patients 1 year of age and older.	This ensures that ferric carboxymaltose injection is prescribed for appropriate patients and that adverse effects are managed optimally and in a timely manner.	The drug must be administered in a setting where appropriate monitoring and management of hypersensitivity reactions can be provided.
Pricing		
5. A reduction in price.	The cost-effectiveness of ferric carboxymaltose is unknown. Based on submitted list prices, ferric carboxymaltose was cost saving in comparison to the total costs of other IV iron therapies. However, there remains uncertainty concerning the comparative safety across iron products and whether potential savings with administration costs	

Reimbursement condition	Reason	Implementation guidance
	compared to ferric derisomaltose will be realized in clinical practice.	
Feasibility of adoption		
6. The feasibility of adoption of ferric carboxymaltose must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given that CDA-AMC was unable to reassess the sponsor's estimate.	—

IV = intravenous.

Discussion Points

- **Criteria for significant unmet need are met**: CDEC noted that ferric carboxymaltose injection is the only IV iron formulation currently approved by Health Canada for use in children and pregnant patients. The committee discussed the clinical expert's observation that pediatric and pregnant patients with IDA who cannot tolerate oral iron or need urgent iron replacement are treated using currently reimbursed IV iron formulations off-label, although clinicians are reluctant to administer an intravenous treatment in children. CDEC noted that the product monographs for ferric derisomaltose and iron sucrose caution against use in pregnancy and potential risk to the fetus based on data from animal studies, and the product monograph for iron sucrose states that it should only be used if the potential benefit outweighs the potential risk to the fetus. Based on these considerations, CDEC concluded that the primary unmet need that ferric carboxymaltose would fill will be in patients who otherwise get off-label treatment with other IV iron formulations, especially in pregnant patients.

- **Indirect assessment of comparative clinical benefit:** CDEC discussed that whereas the sponsor-submitted direct evidence indicated that ferric carboxymaltose was at least as effective as iron sucrose or ferric derisomaltose in improving hemoglobin, ferritin, and TSAT outcomes in patients with IDA, the submitted network metanalysis (NMA) comparing ferric carboxymaltose with other injectable iron formulations had significant limitations, such as inadequate information about study selection and not investigating important efficacy and safety outcomes. Therefore, CDEC could not draw a definitive conclusion from the NMA regarding any clinical advantage of ferric carboxymaltose over the other injectable iron formulations in patients with IDA.

- **Hypophosphatemia risk**: CDEC observed that in the Pivotal Trials and Select RCTs, which provided the central evidence of the CDA-AMC review, the incidences of hypophosphatemia or low blood phosphorus were numerically higher with ferric carboxymaltose than with iron sucrose. The committee noted that the evidence from four RCTs addressing gaps in the pivotal trials and select RCTs demonstrated that the incidence of hypophosphatemia was statistically significantly higher in patients treated with ferric carboxymaltose than in those treated with ferric derisomaltose. CDEC discussed that although the clinical consequences of hypophosphatemia, especially in the long term, were unclear from the reviewed evidence, the drug's Product Monograph notes the risk of hypophosphatemia, hypophosphatemic osteomalacia, and fractures. Of note are fractures that were reported in the post-marketing period, with some requiring surgery. Further, the Product Monograph recommends monitoring for hypophosphatemic osteomalacia in patients who receive multiple doses of ferric carboxymaltose for long-term treatment if they have underlying risk factors, such as vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary hemorrhagic telangiectasia, IBD, and osteoporosis. It is also recommended that serum phosphate levels be checked in patients at risk of low serum phosphate who require a repeat course of treatment within three months.

- **Administration costs:** The cost-savings estimated by the sponsor were entirely driven by reduced administration costs, however, other administrative costs exist (e.g. patient treatment registration/check-in). Clinical input indicates that, in practice, both ferric derisomaltose and ferric carboxymaltose are likely to be administered similarly - specifically, a maximum of 1000 mg per single infusion, with identical infusion and observation times. Consequently, there are unlikely to be any significant differences in administration costs when compared to ferric derisomaltose. As any potential cost-savings are

entirely driven by reduced administration costs, they would not be achieved from a public drug plan perspective as they may pertain to a different budget holder.

- **Adverse events costs:** CDEC noted that the sponsor did not incorporate adverse events into the pharmacoeconomic model despite clinical evidence indicating that there may be an increased risk of hypophosphatemia with ferric carboxymaltose that may require additional monitoring and treatment. CDEC felt that these differences in adverse events may be associated with different resource use costs. If rates of hypophosphatemia requiring treatment and monitoring are higher than assumed in the CDA-AMC reanalysis or if patients develop more severe adverse events (e.g., severe hypophosphatemia, hypophosphatemia osteomalacia and/or fractures), savings associated with the reimbursement of ferric carboxymaltose may be further reduced or eliminated.

Background

Anemia is a medical condition in which the blood has a reduced capacity to carry oxygen due to low hemoglobin (Hb) levels. Anemia has a range of causes. However, iron deficiency (ID) is the most prevalent. Iron deficiency anemia (IDA) results when body iron levels are insufficient to sustain hemoglobin synthesis. The general Canadian population maintains a relatively low prevalence of anemia (~3%). However, the prevalence is higher among Canada's Indigenous population. A 2017 study of the Inuit population in Nunavik (16 years and older) found that the prevalence of anemia was 20% in women of childbearing age, with 14% experiencing IDA and 23% demonstrating ID without anemia. Information for other groups of Indigenous Peoples was not available.

The key goals in treating ID and IDA are correcting the Hb deficit, replenishing iron stores, and maintaining iron levels over time. Oral iron is the first-line Therapy for most ID and IDA and is relatively safe, effective, and inexpensive. According to Mattiello et al., a switch to IV iron is proposed for cases with severe anemia (Hb <70 g/L) to avoid transfusion, for cases with an underlying secondary disease fulfilling a formal indication for IV iron (e.g., inflammatory bowel disease, chronic GI or genitourinary bleeding, coeliac disease), and/or for situations of non-adherence to oral treatment and symptomatic refractory IDA with clinical impact. In instances of severe symptomatic anemia, red blood cell transfusion may be required.

Ferric carboxymaltose injection has been approved by Health Canada for the treatment of iron deficiency anemia in adult and pediatric patients 1 year of age and older when oral iron preparations are not tolerated or are ineffective. It is available as an injection for IV administration, with each mL containing 50 mg of elemental iron. The dosage of ferric carboxymaltose is expressed as mg of elemental iron, with each mL containing 50 mg of elemental iron. The product monograph recommends that a single dose of ferric carboxymaltose should not exceed either 15 mg iron/kg body weight or 1000 mg of iron (20 mL FCM) per week, and dosing follows a stepwise approach based on 1) determination of the individual iron need, 2) calculation and administration of the iron dose(s), and 3) post iron repletion assessments.

The objective of this CDA-AMC's Clinical Review Report is to critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of ferric carboxymaltose 50 mg/mL intravenous infusion for the treatment of IDA in adult and pediatric patients 1 year of age and older when oral iron preparations are not tolerated or are ineffective.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- Clinical evidence from the CDA-AMC review and appraised in the sponsor's submission, including:
    - 2 pivotal studies and 2 other randomized controlled trials (RCTs) in patients with IDA arising from various causes
    - 1 indirect treatment comparison
    - 7 additional studies addressing gaps in evidence
- patients' perspectives gathered by one patient group, the Gastrointestinal (GI) Society
- input from public drug plans that participate in the reimbursement review process
- one clinical specialist with expertise in diagnosing and treating patients with IDA

- a group of 12 clinicians, including those with specialties in cardiology, obstetrics/gynecology, hematology, gastroenterology, and nephrology, and a primary care physician
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

- One patient group, the GI society, provided input to this submission. They obtained input from discussions with health care professionals and researchers, and as well as surveys and interviews conducted on digestive and liver diseases, although the precise number of respondents was not reported.
- The GI society describes dizziness, extreme fatigue, headache, shortness of breath, tiredness and muscle weakness as common symptoms of IDA. IDA can have significant impact on a patient, physically, mentally, financially, and socially, and they emphasized the extreme fatigue that can lead to social isolation.
- The GI society emphasized the tolerability issues associated with oral iron products, and the infusion-related side effects associated with parenteral iron as limitations of treatment. Other limitations include the practical issues associated with having to take time off work and obtain transport to attend infusions.

Clinician Input

Input From the Clinical Expert Consulted for This Review

- The clinical expert consulted by CDA-AMC noted the key limitations of orally administered iron, namely tolerability issues, adherence, and delayed onset of effect. The clinical expert noted the importance of having additional options for parenteral iron, as some patients have tolerability issues. The clinical expert also noted that in many cases, ferric carboxymaltose might be seen as simply another option among several formulations of IV iron.
- The patients most suited for ferric carboxymaltose would be adults with ID or IDA, those unable to tolerate or respond to oral iron, and preoperative patients with IDA, and those least suitable would-be patients with a history of hypophosphatemia according to the clinical expert. The clinical expert did not see any issues with diagnosing IDA, with ferritin and TSAT being key tests of iron stores.
- The clinical expert noted that the key outcomes for assessing response include a rise in Hb, improvement in symptoms of ID and IDA, improved function and reduced transfusion burden. The clinical expert believed that 4 weeks would be the minimum follow-up for assessing efficacy of IV iron supplementation, and 12 weeks would be more ideal.

Clinician Group Input

- A group of 12 clinicians, including those with specialties in cardiology, obstetrics/gynecology, hematology, gastroenterology, and nephrology, as well as a primary care physician provide input.
- The clinician group was in general agreement with the input provided by the clinical expert.
- The clinician group was in agreement with the clinical expert that important unmet needs with IV iron supplementation are the need to reduce visits to the hospital/infusion clinic and to have a product available that has evidence for use in pregnancy.
- The clinician group did not elaborate on their experience with ferric carboxymaltose; however, they did note that it has been available in Europe for 20 years.

Drug Program Input

Input was obtained from the drug programs participating in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for ferric carboxymaltose injection:

- considerations for relevant
- considerations for initiation of therapy
- considerations for continuation or renewal therapy
- considerations for prescribing therapy
- care provision issues
- system and economic issues

The clinical expert consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant Comparators	
Ferric derisomaltose (Monoferric) and iron sucrose (Venofer) were considered comparators by the manufacturer. There were no direct comparative studies in the submission comparing Ferinject to Monoferric. (Monoferric was also compared to iron sucrose. Iron sodium ferric gluconate complex (Ferrliecit) is also a benefit in some jurisdictions. There were a number of clinical trials included in the submission materials. (54 completed interventional clinical studies)	*This is a comment from the drug programs to inform CDEC deliberations.* CDEC noted that although the pivotal trials did not include ferric derisomaltose (Monoferric) as a comparator, the sponsor-submitted additional trials addressing gaps in evidence, include studies that used Monoferric as a comparator. Monoferric was also included in the NMA, although it had limitations that precluded using the results
Due to the need for access to IV infusion centers for administration of IV iron, funding for outpatients may vary between jurisdictions, or funding may be through special programs or provided through health authorities.	*This is a comment from the drug programs to inform CDEC deliberations.*
Considerations for Initiation of Therapy	
Definition of iron deficiency anemia requiring IV iron an vary. For example: in SK the definition of IDA in adult patients is: ○ Hb less than 130g/L; AND ○ Ferritin less than 30mcg/L or transferrin saturation (TSAT) less than 30% OR blood loss greater than 1,000 mL within 7 days. The PM for Ferinject has dosing recommendations for patients with Hb greater than 140g/L. Question for clinical expert: are there specific laboratory parameters thresholds that should be considered for initiation of IV iron?	The clinical expert stated that in the non-CKD, non-CHF, non-oncology population (i.e. generic iron deficiency anemia), the definition of iron deficiency anemia is Hb <130 g/L (males) or <120 g/L (females) AND ferritin <30 (though many clinicians will use ferritin <50 since there is evidence of normalized iron homeostasis when ferritin is >50). Values for Hb also vary in pregnancy (1st and 3rd trimester: <110 g/L; 2nd trimester: <105 g/L) and in children (<24 months: <105 g/L; 24 to 59 months: <110 g/L; 5 to 11 years: <115 g/L). The clinical expert also added the following cutoffs for ferritin and TSAT based on specific conditions: • Inflammation: TSAT <20% and ferritin <100 • CKD: TSAT <30% and ferritin <500

Implementation issues	Response
	• CHF: ferritin <100 mcg/L or ferritin <300 mcg/L with TSAT <20% • Dialysis: ferritin <200 mcg/L or TSAT <20% If iron deficiency is confirmed with anemia, either oral or IV formulations are appropriate (it is a matter of tolerability, time to treatment, accessibility/drug coverage).
Ferinject is the only IV iron product indicated for pediatric patients. Question for CDEC: How are pediatric patients with IDA currently managed? If they cannot tolerate oral iron or need urgent iron replacement, what is the drug of choice for those patients? Ferinject also has an indication specific for Heart Failure (see alternate review) Question for CDEC: Are there patient populations who should not receive Ferinject?	According to the clinical expert, pediatric patients with IDA who cannot tolerate oral iron or need urgent iron replacement are currently treated using any of the existing IV iron formulations (FDI or IS), and it does not appear there are concerns using any of them. The clinical expert also stated that, in their opinion, there are no adult patient populations who should not receive Ferinject
Oral iron is first line and inexpensive. Intolerance to oral iron can be difficult to determine/assess: I.E: Assessment of intolerance: ○ persistence of gastrointestinal side-effects despite having tried tolerability strategies: ○ oral iron has been titrated up from a low dose, ○ utilizing alternate day dosing regimen of oral iron, ○ an adequate trial of at least two different oral iron formulations (e.g. iron salts, polysaccharide iron, heme iron), ○ taking oral iron with small amounts of food, ○ taking oral iron at bedtime. Question for CDEC: How do you define inadequate response to oral iron? What is an appropriate trial of oral iron? Are there populations in which oral iron is inappropriate? (i.e.: bariatric surgery, IBD, CKD, short bowel, etc.?).	The clinical expert noted to CDEC the following: 1. Inadequate response to oral iron: failure to normalize iron stores by 3 months or failure to increment Hb by 10 points in 4 weeks 2. An appropriate minimum trial is 4 weeks. Populations in which oral iron is inappropriate: prior bariatric surgery, gastrectomy, IBD, CKD, prior small bowel resection, CHF, preoperative ID anemia (with 4 weeks or less to surgery), profound iron deficiency anemia (e.g. symptomatic anemia), active malignancy
Hemodialysis patients: Ferinject can be administered during a hemodialysis session. Question for CDEC: What are the benefits of Ferinject over alternatives such as iron sucrose in patients receiving HD? Note: The indication for Monoferric is for patients who have non-hemodialysis dependent chronic kidney disease, and in HD patients the shorter infusion time is not seen as a benefit as chair and nursing time are constant in this patient population.	CDEC noted that Ferinject offers a higher dose of iron infused at each session but agreed there will be no significant benefit if patients are coming regularly for dialysis

Implementation issues	Response
Note: The CDEC recommendation for Monoferric notes that it can be directly injected into the venous limb of a dialyzer.	
Monoferric would occupy a similar therapeutic space; Ferinject is indicated in pediatric patients and HD patients. It also has a specific indication for ID associated with HF.	*This is a comment from the drug programs to inform CDEC deliberations.* CDEC noted that according to the clinical expert, although iron sucrose and Monoferric are not indicated for use in pediatrics, both are used off-label in these patient populations.
Considerations for Continuation or Renewal of Therapy	
Iron deficiency anemia should be assessed and diagnosed through laboratory tests. The dose of Ferinject is determined through a combination of weight and hemoglobin level. Hemoglobin level should be assessed no earlier than 4 weeks after IV iron infusion (to allow erythropoiesis and iron utilization).	*This is a comment from the drug programs to inform CDEC deliberations.*
The reimbursement criteria of other injectable iron products (IDA indication) do not include renewal criteria.	*This is a comment from the drug programs to inform CDEC deliberations.*
Considerations for Prescribing Therapy	
Doses range from 500mg – 2000 mg depending on body weight and hemoglobin level. The maximum dose is 1000 mg per week; patients needing doses on the higher end (i.e. 2000 mg will require a second dose administered a minimum of 7 days from the first dose. Question for clinical expert: Approximately how many patients with IDA will require more than 1 infusion?	The clinical expert stated that at any given time, a minority of patients will receive more than 1 g, though it is frequent for individuals to require longstanding treatment (e.g., IV iron q3 months).
Ferinject is a high-dose IV iron preparation which can be administered in 15 minutes (compared to 30 minutes for Monoferric). Ferinject can be administered by injection or by IV infusion, or directly into the dialyzer.	*This is a comment from the drug programs to inform CDEC deliberations.*
Care Provision Issues	
The Drug is administered intravenously, and patient monitoring is required for signs and symptoms of hypersensitivity reactions during administration and for at least 30 minutes for each administration.	*This is a comment from the drug programs to inform CDEC deliberations.*
System and Economic Issues	
a. Involvement of additional payers	*This is a comment from the drug programs to inform CDEC deliberations.*

Implementation issues	Response
Proper management of IDA may lead to reduced requirement for blood products which are funded outside of the Drug Plan.	
b. Presence of confidential negotiated prices for comparators Monoferric was successfully negotiated through pCPA.	*This is a comment from the drug programs to inform CDEC deliberations.*
c. Special programs or initiatives for the introduction and management of the drug(s) under review Anemia management programs may exist in certain jurisdictions.	*This is a comment from the drug programs to inform CDEC deliberations.*
d. Other systems or economic issues Savings from reduced chair time are likely not realized, but there is potential for increased capacity (i.e.: more patient access).	*This is a comment from the drug programs to inform CDEC deliberations.*

CHF = congestive heart failure; CKD = chronic kidney disease; IBD = inflammatory bowel disease; IDA = iron deficiency anemia; IV = intravenous; NMA = network metanalysis; TSAT = transferrin saturation.

Clinical Evidence

Pivotal Studies and Select RCTs

Description of Studies

The systematic review portion of this report focused on four studies: the two pivotal Phase 3 RCTs per the Health Canada review (VIT-IV-CL-015 and FERGIcor) and two Phase 3 RCTs (1VIT05006 and VIT-IRON-2011-004) selected from the sponsor's submitted systematic review. The pivotal trials focused on specific populations, patients with CKD (VIT-IV-CL-015, N=240) and with IBD (FERGIcor, N=304), with each study randomizing patients 1:1 to either ferric carboxymaltose and iron sucrose. Studies 1VIT05006 and VIT-IRON-2011-004 that included a more heterogeneous IDA population (i.e., patients had IDA arising from various causes), 1VIT05006 (N = 559) was a placebo-controlled study with a crossover design and VIT-IRON-2011-004 (N=371) was a non-inferiority study that randomized patients 1:1 to either ferric carboxymaltose or iron sucrose. The primary outcome in 3 of the trials was to assess Hb response, as an increase from baseline. The 1VIT05006 trial was not designed to assess efficacy outcomes.

In FERGIcor, the mean (standard deviation [SD]) age was 52.7 (13.8) years in the ferric carboxymaltose group and 51.0 (12.6) years in the iron sucrose group, while in VIT-IV-CL-015 and in the other studies the mean age was around 40 years. In VIT-IV-CL-015 approximately 42% of patients were female and in FERGIcor 59% were female. In the non-pivotal trials enrolling patients with IDA arising from various causes, approximately 90% of all the patients were female. Overall mean Hb was 93.2 g/L in VIT-IV-CL-015, 102.2 g/dL in FERGIcor, [redacted] g/L in 1VIT05006, and less than 80 g/L in VIT-IRON-2011-004.

Efficacy Results

Hospitalizations (all-cause and anemia related)

This outcome was not assessed in any of the 4 trials that were the focus of this systematic review section.

Hemoglobin

In VIT-IV-CL-015 the primary response rate was defined as the percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks after baseline. The percentage of responders in the ferric carboxymaltose group was 45/97 (46.4%) and in the iron sucrose group 32/86 (37.2%) with a reported p-value for the between-group difference of p=0.2101. The mean increase of Hb in the ferric

carboxymaltose group at week 4 was [redacted] and in the iron sucrose group [redacted] with a reported p-value for the between-group difference of [redacted]. No between-group difference with confidence interval was reported for either end point.

In FERGIcor, the primary outcome was responders with at least 20 g/L increase in Hb at Week 12. In the full analysis set (FAS), the percentage of responders was 65.79% (n = 150/240) in the ferric carboxymaltose group and 53.64% (n = 118/220) in the iron sucrose group. The between-group difference was 12.15% (95% CI 3.07, 20.97), p=0.004, higher in the ferric carboxymaltose group compared with the iron sucrose group. The FAS set was also analyzed using last observation carried forward (LOCF) and the worst-case method and the results were consistent with the primary analysis.

In VIT-IRON-2011-004, 99.5% (n=184/185) of patients in each of the ferric carboxymaltose and 98.3% (n=177/180) of patients in the iron sucrose group achieved an increase in Hb of at least 20 g/L from baseline to week 8 for a between-group difference of 1.13 (95% CI: −2.02 to 4.68). The criteria for non-inferiority were met. From a mean (SD) baseline of 77.4 g/L (14.95) in the ferric carboxymaltose group and 80.5 g/L (14.45) in the iron sucrose group, the mean (SD) change from baseline to week 8 was [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group. The between-group difference was [redacted]

Patient-reported HRQoL

In FERGIcor, for the Physical component of the SF-36, from a mean (SD) baseline of 44.17 (7.36) in the ferric carboxymaltose group and 44.98 (7.23) in the iron sucrose group, there was a change from baseline to week 12 of 3.88 (6.77) and 2.64 (7.14), respectively for a reported between-group p value of p=0.157. For the Mental component of the SF-36, from a mean (SD) baseline of 40.02 (11.04) in the ferric carboxymaltose group and 41.30 (11.70) in the iron sucrose group, there was a change from baseline to week 12 of 5.91 (10.74) and 5.56 (10.36), respectively, for a between-group p-value of p=0.583. For the IBDQ total score, from a mean (SD) baseline of 150.8 (35.2) in the ferric carboxymaltose group and 152.7 (34.4) in the iron sucrose group, there was a change from baseline to week 12 of 21.1 (32.3) and 19.7 (28.8), respectively, for a between-group p-value of p=0.872. Between-group differences with confidence intervals were not reported for any of the HRQoL measures.

HRQoL was not assessed in VIT-IV-CL-015 or VIT-IRON-2011-004.

Serum ferritin

In VIT-IV-CL-015 the mean baseline was [redacted]) in the ferric carboxymaltose group and [redacted] in the iron sucrose group. After week 4, there was a change from baseline of [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group, with a reported between-group p-value of [redacted]. The between-group difference with confidence interval was not reported.

In FERGIcor, the mean (SD) baseline was [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group. After week 4, there was a change from baseline of [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group for an estimated difference between groups (repeated measures analysis) of [redacted]

In VIT-IRON-2011-004, the mean (SD) baseline of [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group. After week 8, there was a change from baseline of [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group, for a LS mean between groups of [redacted]

Transferrin saturation (TSAT)

In VIT-IV-CL-015, there were [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group who had a normal TSAT of between 20% and 50% by week 4, for a reported between-group p-value of [redacted]. The between-group difference with confidence interval was not reported.

In FERGICor, there were 117/222 patients (52.7%) in the ferric carboxymaltose group and 76/209 patients (36.4%) in the iron sucrose group with a normal TSAT level (20%-50%) at week 12. The odds ratio was 2.05 (95% CI 1.37, 3.06), p<0.001, in favour of ferric carboxymaltose. The absolute between-group difference with confidence interval was not reported.

TSAT response (achieving a normal TSAT) was not assessed in VIT-IRON-2011-004.

Non-anemic patients

For non-anemic patients in the FERGIcor trial, (Hb level of ≥120 g/L for females or ≥130 g/L for males), the percentage of responders at Week 12 was 72.8% (166/228) in the ferric carboxymaltose group and 61.8% (136/220) in the iron sucrose group. The odds ratio was 1.65 (95% CI 1.10, 2.46) p=0.015. The absolute between-group difference with confidence interval was not reported.

Harms Results

Adverse Events

In the overall study population in VIT-IV-CL-015, [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group had at least one AE. In FERGIcor there were AEs in [redacted] patients in the ferric carboxymaltose group and in [redacted] patients in the iron sucrose group.

In the overall study population in 1VIT05006, [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the placebo group reported at least one AE. In VIT-IRON-2011-004 there were [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group who had AEs.

Serious Adverse Events

In VIT-IV-CL-015 SAEs were reported in [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group. In FERGIcor there were SAEs in [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group.

In 1VIT05006, [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the placebo group had an SAE. In VIT-IRON-2011-004 [redacted] patients [redacted] in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group had an SAE.

Withdrawals Due to Adverse Events

In VIT-IV-CL-015, [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group withdrew from study medication due to AEs. In FERGIcor 7 (2.9%) patients in the ferric carboxymaltose group and 2 (0.8%) patients in the iron sucrose group withdrew from the study drug due to an AE.

In 1VIT05006, [redacted] patient in the ferric carboxymaltose group and [redacted] patients in the placebo group withdrew from study medication due to an AE. In VIT-IRON-2011-004 [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group withdrew from study medication due to an AE.

Mortality

Across the studies, [redacted] patient in the ferric carboxymaltose group died during VIT-IV-CL-015 due to acute anterior myocardial infarction. [redacted] died more than a week after study medication was withdrawn due to a non-serious AE. In 1VIT05006, [redacted] patient in the ferric carboxymaltose group died due to pneumonia. There were no deaths reported in the other 2 studies.

Notable Harms

In FERGIcor, hypophosphatemia was observed in 6 (2.5%) patients in the ferric carboxymaltose group (and none were observed in the iron sucrose group. Hypophosphatemia was not reported in VIT-IV-CL-015.

In VIT-IRON-2011-004, hypophosphatemia was observed in [redacted] ferric carboxymaltose patients [redacted] and in [redacted] patients [redacted] in the iron sucrose group. Patients with decreased blood phosphorous or hypophosphatemia was not reported in 1VIT05006.

Critical Appraisal

- None of the active-controlled trials were blinded, and this may bias assessment of patient-reported outcomes such as HRQOL as well as the assessment of subjective harms. One of the three studies did not plan for any formal comparisons between ferric carboxymaltose and iron sucrose, while the other two studies did not implement a multiple testing procedure,

thus increasing the risk that statistically significant results (beyond the primary outcome) were false positives. There were fewer patients in the ferric carboxymaltose group compared to the iron sucrose group who withdrew from VIT-IV-CL-015 ([redacted]), and this may also bias assessment of efficacy and harms in this relatively short (4 weeks) study. Between-group differences with confidence intervals were infrequently reported, limiting judgments about the precision of the effect estimates.

- There were few if any patients in the included studies who identified as Indigenous, and this is an important gap considering there is a disproportionate number of patients with IDA in Canada who are Indigenous. While one of the pivotal studies, FERGIcor, assessed HRQOL, the other studies did not, and there were no studies that formally assessed the impact of ferric carboxymaltose on fatigue and other important outcomes in this patient population.

GRADE Summary of Findings and Certainty of the Evidence

In the absence of a complete body of evidence for any patient population or comparison, no GRADE assessment was performed for this review.

Long-Term Extension Studies

There were no long-term extension studies submitted by the sponsor.

Indirect Comparisons

The sponsor submitted a summary of indirect evidence from a published NMA that compared the effects of ferric carboxymaltose with other intravenous iron therapies in the context of adults with iron deficiency anemia associated with inflammatory bowel disease.

Description of Studies

The NMA submitted by the sponsor included 5 RCTs. All studies were performed in patients with inflammatory bowel disease. The interventions in the studies included ferric carboxymaltose, iron sucrose, iron isomaltoside (also known as ferric derisomaltose) and oral iron.

Efficacy and Harms Results

Point estimates for the odds ratios comparing ferric carboxymaltose with ferric derisomaltose and iron sucrose favoured ferric carboxymaltose; however, the 95% credible intervals (CrIs) were wide and included effects favouring the comparator interventions, and no difference. Harms were not assessed in the NMA. Therefore, the summary of the published NMA submitted by the was insufficient to determine whether there is a difference in efficacy or harms for ferric carboxymaltose compared to other injectable forms of iron in patients with iron deficiency anemia and inflammatory bowel disease.

Critical Appraisal

The sponsor selected a published NMA that used a Bayesian approach with fixed effects models for the analyses. Limited information is available regarding the methods used in the NMA model. The NMA was informed by a systematic review of relevant databases, although the search may not have been exhaustive. The date last searched was June 2016, over 8 years ago at the time of writing this report. Relevant studies available since this time would have been excluded from the analyses. The authors performed an assessment of bias for the included studies but did not explain how the results of this assessment were incorporated into the analyses. It was not clear if the authors incorporated an assessment of clinical heterogeneity into their analyses.

Another limitation of the NMA is that it contained a small amount of data from 5 studies resulting in a network with only one or two studies connecting the nodes and wide credible intervals. Only one outcome was assessed in the NMA. There was no analysis of harms or other outcomes that are important for patients.

There was heterogeneity in the time point for end point evaluation which could have biased the results. Few patient characteristics were reported across the trials, challenging a thorough assessment of the plausibility of the exchangeability assumption. Interpretation of the effect estimates was limited by imprecision. The 95% CrIs for the comparisons of ferric carboxymaltose and

ferric derisomaltose and iron sucrose were wide and included the potential for no difference, or that either treatment could be favoured.

Another significant limitation is related to the sponsors lack of clear, a priori criteria for selecting the NMA by Aksan et al. There are at least two others published NMAs investigating the relative efficacy of ferric carboxymaltose in broader iron deficiency anemia populations. There was no protocol outlining a priori how one or more NMAs would be selected for presentation among multiple NMAs reporting on the same population, comparisons, and outcomes. As such, there is risk of bias in the selection of the NMA.

Summary of ITC

The summary of a published NMA submitted by the manufacturer was insufficient to determine whether there is a difference in efficacy for ferric carboxymaltose compared to other injectable forms of iron in patients with iron deficiency anemia and inflammatory bowel disease. Important efficacy and harms outcomes were not investigated.

Studies Addressing Gaps in the Evidence from Pivotal Studies and Select RCTs

This section presents additional evidence from 6 studies that address gaps in the evidence from Pivotal Trials and Select RCTs: 1 study in pediatric patients, 1 study in patients with IDA resulting from various causes, and 4 studies comparing ferric carboxymaltose with ferric derisomaltose in patients with IDA.

The 1VIT17044 trial

The 1VIT17044 trial is a phase III, multicentre, randomized, active controlled, open-label clinical trial conducted in 30 sites across 4 countries (the US, Ukraine, Poland, and Canada). The trial enrolled 79 patients who were assigned to receive ferric carboxymaltose (n = 40) or oral iron (n = 39). The trial aimed to investigate the efficacy and safety of ferric carboxymaltose versus oral iron in pediatric patients with IDA and a documented history of inadequate response to oral iron. In the 1VIT17044 trial, the least-square mean change in Hb from baseline to Day 35 obtained through the ANCOVA model was 2.22 g/dL [redacted] in the ferric carboxymaltose and 1.92 g/dL [redacted] in the oral iron group. The treatment difference at Day 35 was 0.30 g/dL (95% CI: -0.28, 0.88) (p-value=0.3108). The results of the MMRM model and the subgroup analyses align with the main analysis. The least-square mean change in ferritin from Baseline to Day 35 obtained through the ANCOVA model was [redacted] in the ferric carboxymaltose and [redacted] in the oral iron group. The treatment difference at Day 35 was [redacted]. The least-square mean change in transferrin saturation from Baseline to Day 35 obtained through the ANCOVA model was [redacted] in the ferric carboxymaltose and [redacted] in the oral iron group. The treatment difference at Day 35 was [redacted]. In the 1VIT17044 trial, a larger percentage of participants in the ferric carboxymaltose group than in the oral iron group experienced at least one TEAE [redacted] vs. [redacted] Numerically more patients in the ferric carboxymaltose group than the oral iron group experienced metabolism and nutrition disorders ([redacted]) and hypophosphatemia ([redacted]). Numerically fewer patients in the ferric carboxymaltose group than the oral iron group experienced gastrointestinal disorders ([redacted]) and constipation ([redacted]). One patient in the FCM group experienced a TEAE that led to treatment discontinuation. None of the patients experienced any serious AE or any TEAE leading to death.

Critical Appraisal

Internal Validity

Although the methods for randomization were likely appropriate, due to the small sample size there is an increased risk that prognostic balance was not achieved, as evidenced by imbalances in patients' baseline disease and demographic characteristics. Notably, the baseline serum ferritin level was higher in oral iron arm. There were also baseline imbalances by ethnicity and by BMI. The effect of these differences on efficacy outcomes is unclear. The trial was open label, however the efficacy outcomes are objective, so it is unlikely that bias was introduced in their measurement. There is a risk of bias in the reporting of subjective harms (e.g., gastrointestinal disorders, headache) because patients knew to which treatment they were assigned (e.g., it is possible that known harms could be overestimated). The authors used the LOCF method to impute missing outcomes data and conducted sensitivity analyses using MMRM under the missing at random assumption. Although neither method may be appropriate (LOCF may not be reflective of the true trajectory of the outcome, and MMRM assumes data are missing at random, which is not possible to assess and may not be plausible), the attrition rate was low (5% of less) in each group. As such, it is unlikely that missing data would

have introduced bias. The ITT analysis was appropriate for estimating the effect of assignment to the interventions. Because there were no adjustments for multiple comparisons, there is an increased risk of type 1 error (false positives) for statistically significant results. Although the subgroup analyses were pre-planned, these were unlikely powered to detect subgroup differences.

External Validity

The included patients are from age group of 1 to 17 and results are not generalizable to other age groups. Further, given the small sample size, it is unlikely that the results would be broadly generalizable to all pediatric patients with IDA. As the comparator in the trial was oral iron, this study does not inform about the efficacy or harms of ferric carboxymaltose relative to other IV iron formulations in pediatric patients. Indigenous Peoples, who are disproportionately affected by IDA, are not represented in this trial. Although the outcomes measures were appropriate, some outcomes that may be important to patients (e.g., HRQoL) were not reported.

The 1VIT09031 trial

The 1VIT09031 trial is a phase III, multi-centre, randomized, active controlled, open -label study to investigate the efficacy and safety of intravenous ferric carboxymaltose in adult patients with IDA who had an unsatisfactory response or intolerance to oral iron. Cohort assignment was based on results from a 14-day run-in period with oral iron. Patients with inadequate response to oral iron (Hb increase <1 g/dL) were assigned to Cohort 1, and patients who were intolerant of oral iron were assigned to Cohort 2. Oral iron was the comparator arm in Cohort 1, and other IV iron standard of care (SC) per investigator's choice was the comparator in Cohort 2. In Cohort [redacted] patients received ferric carboxymaltose and [redacted] received oral iron. In Cohort 2, [redacted] patients received ferric carboxymaltose and [redacted] received IV SC. Patients were followed up to Day- 35 for efficacy assessment, and up to Day- 120 for safety assessment. For the protocol-specified primary treatment group comparison (Cohort 1), the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or TOI was 1.57 g/dL [redacted] in Group A (ferric carboxymaltose) and 0.80 [redacted] in Group B (oral iron) (P = 0.001). No between-group difference with confidence interval was reported. In a post-hoc comparison of Group C (ferric carboxymaltose) versus Group D (IV SC) (Cohort 2), the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or TOI was 2.90 g/dL [redacted] in Group C (ferric carboxymaltose) and 2.16 [redacted] Group D (IV SC). No between-group difference with confidence interval was reported. Subgroup analysis revealed the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention was greater for the FCM group than the comparator group regardless of baseline hemoglobin value or etiology of IDA.

In Cohort 1, the proportion of patients achieving Hb >12.0 g/dL was [redacted] in the FCM group and [redacted] in the oral iron group (P < [redacted]). The proportion of patients with a clinically meaningful increase in Hb (as defined by the investigators) was [redacted] in the FCM group and [redacted] in the oral iron group (P < [redacted]). The proportion of patients with a Hb >12 g/dL and ferritin increase ≥160 ng/mL was [redacted] in the FCM group and [redacted] in the oral iron group (P < [redacted]). The mean change in Hb was [redacted] g/dL (SD = [redacted]) in the FCM group and [redacted] g/dL (SD = [redacted]) in the oral iron group (P < [redacted]). The mean change in ferritin was [redacted] ng/mL (SD = [redacted]) in the FCM group and [redacted] ng/mL (SD = [redacted]) in the oral iron group (P < [redacted]). The mean change in TSAT was [redacted] (SD = [redacted]) in the FCM group and [redacted] (SD = [redacted]) in the oral iron group (P < [redacted]). Between-group differences with confidence intervals were not reported for any outcome.

In Cohort 2, the proportion of patients achieving Hb >12.0 g/dL was [redacted] in the FCM group and [redacted] in the IV iron group (P < [redacted]). The proportion of patients with a clinically meaningful increase in Hb (as defined by the investigators) was [redacted] in the FCM group and [redacted] in the IV iron group (P < [redacted]). The proportion of patients with a Hb >12 g/dL and ferritin increase ≥160 ng/mL was [redacted] in the FCM group and [redacted] in the IV iron group (P < [redacted]). The mean change in Hb was [redacted] g/dL (SD = [redacted]) in the FCM group and [redacted] g/dL (SD = [redacted]) in the IV iron group (P < [redacted]). The mean change in ferritin was [redacted] ng/mL (SD = [redacted]) in the FCM group and [redacted] ng/mL (SD = [redacted]) in the IV iron group (P < [redacted]). The mean change in TSAT was [redacted] (SD = [redacted]) in the FCM group and [redacted] (SD = [redacted]) in the oral iron group (P < [redacted]). Between-group differences with confidence intervals were not reported for any outcome.

There were numerically more TEAEs in Group A ([redacted] compared with Group B ([redacted] Overall rates of TEAEs were similar between Group C (ferric carboxymaltose) and D (IV SC) ([redacted] across groups). The most commonly (≥5%) experienced TEAE in Group A was nausea ([redacted]%), in Group C was hypophosphatemia ([redacted]%), and in Group D was dizziness ([redacted]%). No TEAE was experienced in ≥5% of patients in Group B. [redacted] ([redacted]%) patients in Group A (ferric carboxymaltose), [redacted] pateints in Group B (oral iron), [redacted] patients in Group C (ferric carboxymaltose), and [redacted] patients in Group D (IV iron) experienced at least 1 serious adverse event during the Treatment Phase. [redacted] patients in Group A (ferric carboxymaltose) and [redacted] in the Group B (oral iron) experienced hypersensitivity reactions. [redacted] patients in Group C (ferric carboxymaltose) and [redacted] in Group D (IV iron) experienced hypersensitivity reactions.

Hypersensitivity reactions in the ferric carboxymaltose patients were either Grade 2 or 3, and in the IV SC arm were Grades 1-3. [redacted] patients in Group A (ferric carboxymaltose) and [redacted] in Group B (oral iron) experienced skin and subcutaneous tissue disorders. [redacted] patients in Group C (ferric carboxymaltose) and [redacted] in group D (IV iron) experienced skin and subcutaneous tissue disorders. All TEAEs associated with skin and subcutaneous tissue disorders SOC (erythemia, pruritus, rash, rash maculopapular, urticaria) were either Grade 1 or 2. In Group A (ferric carboxymaltose [redacted] of patients experienced hypophosphatemia and [redacted] experienced potentially clinically significantly (PCS) low phosphorus compared with [redacted] in Group B (oral iron), respectively. In Group C (ferric carboxymaltose), [redacted] of patients experienced hypophosphatemia and [redacted] experienced PCSlow phosphorus compared with [redacted] in Group D (IV SC), respectively. Hypophosphatemia was mainly Grade 1 to 3 in severity, with a single Grade 4 event. Most PCS low phosphorus events were Grade 3, with [redacted] Grade [redacted] events in patients in the ferric carboxymaltose group. No PCS low phosphorus events were associated with serious or severe AEs. [redacted] patient had events of somnolence, fatigue, tingling finger, swollen hand, and elevated WBC count on days when phosphorus was Grade 4. In total [redacted] deaths reported in the study, [redacted] in Group B (oral iron), [redacted] in Group C (ferric carboxymaltose), and [redacted] in Group D (IV iron). None were considered related to study drug by investigator.

Critical Appraisal

Internal Validity

Although the methods for randomization and allocation concealment appeared adequate, there were imbalances at baseline in some important clinical characteristics. Most notably, serum ferritin was higher in Group C (ferric carboxymaltose) compared with Group D (IV SC). It is not certain if this imbalance may have biased the results. The trial was open-label, however the efficacy outcomes are objective so it is unlikely that bias was introduced in their measurement. There is a risk of bias in the reporting of subjective harms because patients knew to which treatment they were assigned (e.g., it is possible that known harms could be overestimated). Across groups, up to [redacted] of patients did not complete the study and methods for handing missing data are not clear. As such, there is a risk of bias due to missing outcomes data, but the extent and direction of the bias cannot be predicted. The mITT analysis was appropriate for estimating the effect of assignment to the interventions. Although the mITT population was a subset of the ITT population, few patients were excluded from the mITT analysis set (less than 4% across groups). Because there were no adjustments for multiple comparisons, there is an increased risk of type 1 error (false positives) for statistically significant results. Between-group differences with confidence intervals were not reported for any outcome, precluding judgments about the precision of the effects.

External Validity

In this study, all patients received two doses of 15 mg/kg, up to a maximum single dose of 750 mg and a maximum cumulative dose of 1500 mg. These values were all lower than recommended dosing in the PM, which recommends a maximum single relative dose of 20 mg/kg, a maximum single absolute dose of 1000 mg, and a maximum total dose of 2000 mg. In Group D, patients could have been assigned to any of 5 IV iron formulations, only 2 of which were considered relevant comparators for this review. As such, the generalizability of the results may be limited. Further, the comparison of Group A (ferric carboxymaltose) to Group B (oral iron) does not inform about the efficacy and harms of ferric carboxymaltose relative to other IV oral formulations available in Canada, limiting the applicability of these results. The study conducted in 84 US centres only, with no patients from Canada and no representation of Indigenous Peoples, who are disproportionately affected by IDA. As only adults were enrolled in the study, it is uncertain whether the results could be generalized to pediatric patients. Further, for Group A (ferric carboxymaltose) and Group B (oral iron) the study selected patients based on adherence to oral iron following a run-in phase and a large proportion of these patients ([redacted]) were not enrolled. As such, the enrolled patients may not be representative of patients seen in clinical practice (as patients with lower adherence were not enrolled). Although relevant outcomes were investigated in the study, other outcomes that may be important to patients (e.g., HRQoL) were not investigated.

Zoller 2023

Zoller 2023 is a multicentre, randomized, double-blind, active controlled, clinical trial conducted at 20 outpatient hospital clinics in Austria, Denmark, Germany, Sweden, and the UK. The trial compared the incidence of hypophosphatemia after treatment with ferric carboxymaltose (N=48 patients) versus ferric derisomaltose (N=49 patients) in 97 patients with IDA and IBD. By Day 70 (the end of the trial), level of ferritin and TSAT increased in both treatment groups. Hb increase by Day 70 in the ferric derisomaltose group was 24.9 g/L (95% CI 21.1 to 28.8) and in the ferric carboxymaltose group was 25.2 g/L (95% CI 21.3 to 29.1). The between group difference with confidence interval was not reported for any efficacy outcome. Both ferric derisomaltose and ferric carboxymaltose

resulted in improvement in fatigue symptoms and increased FACIT Fatigue Scale scores (possible scores ranging from 0 to 52), which was statistically significantly greater for patients treated with ferric derisomaltose versus ferric carboxymaltose at Days 35 and 49. The between-group difference with confidence interval was not reported at any follow up time point.

Numerically, more patients experienced hypophosphatemia and vitamin D deficiency in the ferric carboxymaltose group compared with ferric derisomaltose group (hypophosphatemia: 28.6% vs. 2.1% and Vit D deficiency: 34.7% vs. 22.9%, respectively). Numerically, fewer patients experienced headache and nausea in the ferric carboxymaltose group compared with the ferric derisomaltose group (headache: 10.2% vs. 18.8% and nausea: 2.0% vs. 12.5%, respectively). Discontinuation due to adverse events occurred among 6.3% of patients in ferric derisomaltose group and 2.0% of patients in the ferric carboxymaltose group. There were no deaths in the trial. Hypophosphatemia in this trial was defined as serum phosphate level of less than 2.0 mg/dL. The primary endpoint was the incidence of hypophosphatemia at any time after the first dose to Day 35, which was reported as 8.3% (n=4/48) in the ferric derisomaltose group and 51.0% (n=25/49) in the ferric carboxymaltose group with adjusted risk difference of −42.8% (95% CI –57.1 to –24.6) favouring ferric derisomaltose; p<0.0001. The majority of patients recovered from hypophosphataemia by Day 70. In an analysis by diagnosis of IBD, the risk differences were 43.1% and 45.5% higher in the ferric carboxymaltose group for patients with ulcerative colitis and Crohn's disease, respectively (interaction P value = 0.1948). The highest incidence of hypophosphatemia occurred within 2 weeks of treatment in both arms. The secondary safety endpoint was the incidence of hypophosphatemia at any time from baseline to Day 70, which occurred among 12.5% (n=6/48) of patients in the ferric derisomaltose group and 59.2% of patients (n=29/49) in the ferric carboxymaltose group with adjusted risk difference of −46.6% (95% CI −60.9% to –28.1%), favouring ferric derisomaltose; p<0.0001. Per the investigators, the mean decreases in phosphate concentration from baseline after the first and second doses were significantly greater after ferric carboxymaltose infusion compared to ferric derisomaltose infusion (between-group differences with confidence intervals were not reported). For more than 1 month after the second infusion 4.7% (n=2/43) of patients in the ferric carboxymaltose group remained hypophosphataemic. On Day 70 the mean serum phosphate remained significantly lower in ferric carboxymaltose group compared to ferric derisomaltose group (between-group differences with confidence intervals were not reported).

Critical Appraisal

Internal Validity

Although the methods for randomization appeared appropriate, due to the small sample size there is an increased risk that prognostic balance was not achieved, as evidenced by imbalances in some baseline disease and demographic characteristics. Notably, there were imbalances at baseline in IBD diagnosis (Crohn's disease or ulcerative colitis). The use of some concomitant medications (e.g., interleukin inhibitors and vitamin D supplements) were also imbalanced between groups. The effect of these differences on the efficacy and safety results is uncertain. Although the absolute risk differences for hypophosphatemia among patients with Crohn's disease and ulcerative colitis who were treated with ferric carboxymaltose versus ferric derisomaltose were similar (and the interaction P value was not statistically significant), the subgroups were small, and the analysis likely not powered to detect subgroup differences. As the trial was double-blinded and methods to maintain the blinding appeared adequate, there is likely low risk of bias in the measurement of the outcomes. Considering the importance of patient reported outcomes the use of FACIT Fatigue Scale which is a reliable and valid instrument for measuring fatigue in IBD was appropriate. [23] Since the trial was double-blinded the risk of bias due to reporting subjective patient reported outcomes is low. However, since the between-group difference with confidence interval was not reported at any follow up time point, it precludes judgments about the precision of the effects. For the analysis of hypophosphatemia, 2 patients in the ferric derisomaltose group and 1 patient in the ferric carboxymaltose group did not have a postbaseline observation and were imputed as having hypophosphatemia in the primary analysis. As the proportion of patients with missing data was low for this outcome, there is likely low risk of bias due to missing outcomes data. Further, a post-hoc sensitivity analysis where these patients were imputed as either being free of hypophosphatemia or were excluded yielded similar results to the primary analysis. There was no imputation of missing values in this trial except for the change from baseline in patients with no postbaseline measurements which was set to zero at the first postbaseline visit. Further, the attrition rate was 10% in ferric derisomaltose group and 12.5% in ferric carboxymaltose group, as a result, risk of bias due to missing data is not high. Statistical analyses in this trial were not adjusted for multiple comparisons. As such, there is an increased risk of false positive conclusions for statistically significant results. Particularly for efficacy outcomes (e.g., change in Hb, ferritin, TSAT, and fatigue) between-group

differences with confidence intervals were not reported, precluding conclusions about the magnitude (including clinical importance) of the estimated effects and their precision.

External Validity

All patients enrolled in this trial had IBD; however, given the small sample size of the trial the results may not be broadly generalizable. The length of follow-up was relatively short, which limits conclusions about efficacy and safety over a longer period and among patients who require chronic treatment with IV iron. Although the efficacy outcomes measured were appropriate, due to insufficient reporting of between-group differences and confidence intervals, conclusions about the magnitude of the estimated effects and their precision were limited. Indigenous Peoples, who are disproportionately affected by IDA, were not represented in this study. In this trial patients received a single IV infusion of 1000 mg at baseline (Day 0) and, depending on the a priori calculated iron dose, either 500 mg or 1000 mg at Day 35. According to the product monograph for ferric carboxymaltose a single dose should not exceed 15 mg iron/kg body weight or 1000 mg of iron. Based on Product monograph for ferric derisomaltose [24] allowable iron dose per infusion is limited to 20 mg iron/kg body weight. Seems the dosage administered in this trial aligned with the product monographs.

Emrich 2020

Emrich 2020 is a prospective, single-center, double-blind study. The study randomized 26 women with IDA to receive ferric carboxymaltose (N = 13 patients) group and in the ferric derisomaltose (n = 13 patients). This trial aimed to assess hypophosphatemia after high-dose iron repletion with ferric carboxymaltose and ferric derisomaltose. The trial assessed quality of life by Short Form 36 Health Survey (SF-36), functional impairment by Sheehan disability scale, and fatigue by the German version of The Multidimensional Fatigue Inventory (MFI) but the results have not been published. Change in the level of Hb, ferritin and TSAT were not among the trial endpoints and were not reported. The primary outcome was hypophosphatemia at any post-infusion study visit. It was reported in 75% (9 of 12) of the patients in the ferric carboxymaltose group and 8% (1 of 13) of the patients in the ferric derisomaltose group, as measured at study visit 4 (days 5 to 9) (p = 0.001). At study visit 5 (days 33 to 37), 25% (n = 3/12) and 8% (n = 1/13) of patients in the ferric carboxymaltose and ferric derisomaltose groups, respectively, had hypophosphatemia. The between-group difference with confidence interval was not reported at any follow-up time point.

Critical Appraisal

Internal Validity

The methods of randomization appeared appropriate, however there are imbalances in some baseline characteristics which might be due to the small sample size. Further, due to logistic reasons after the inclusion of 26 patients (instead of estimated 30 to achieve 80% power) the interim analysis was conducted and the trial completed after interim analysis, therefore, there is the possibility that if more patients had been enrolled then the effect size may have been differed. Due to lack of information in the publication the adequacy of blinding is unclear. Only one patient was excluded from the analyses, therefore the risk of bias due to missing data is low. There is an increased risk of false positive conclusions for statistically significant results, since statistical analyses were not adjusted for multiple comparisons. The between-group differences with confidence intervals were not reported for the primary outcome of hypophosphatemia which precludes conclusions about the magnitude of the estimated effect and its precision.

External Validity

Given the small sample size of the trial and considering that all patients enrolled in this trial were female and Caucasians the results may not be broadly generalizable. Further, the results also are not generalizable to the patients with conditions that were excluded from the study such as advanced chronic kidney disease, pregnancy, ongoing lactation, untreated hyperparathyroidism, hemochromatosis, active malignancy, bronchial asthma, atopic dermatitis, active alcohol or drug abuse, history of a psychological illness or seizures. The length of follow-up was relatively short, which limits conclusions about the safety result (hypophosphatemia) over a longer duration. In this trial only one infusion was performed which limits detection of consequences of repeated infusions.

Wolf 2020

Wolf 2020 reports on 2 identically designed, open label, randomized clinical trials which aimed to assess effects of ferric carboxymaltose and ferric derisomaltose on hypophosphatemia. In trial A, 123 patients were randomized to receive ferric carboxymaltose (N = 61patients) or ferric derisomaltose (N = 62 patients). In trial B 122 patients were randomized to receive ferric carboxymaltose or ferric derisomaltose (N=61 patients in each group). In total 122 patients were randomized to receive ferric carboxymaltose and 123 to receive ferric derisomaltose. The results of Hb, ferritin and TSAT from trial A and B are presented, however, changes from baseline and between-group differences with confidence intervals were not reported for Hb, ferritin and TSAT outcomes at any time point.

Overall, in the ferric carboxymaltose vs. the ferric derisomaltose groups, 27/60 (45.0%) vs 7/63 (11.1%) patients in trial A and 28/57 (49.1%) vs 14/62 (22.6%) in trial B experienced adverse events. Serious or severe hypersensitivity reactions occurred in 1 patient (0.8%) in the ferric derisomaltose group (swollen eyelid unilaterally) and in 2 patients (1.7%) in the ferric carboxymaltose group (dyspnea and swelling). Regarding the specific adverse drug reaction, in the ferric carboxymaltose vs. the ferric derisomaltose groups, 12 (20.0) vs 0 patients in trial A and 7 (12.3) vs 0 in trial B experienced decreased blood phosphorus. In the ferric carboxymaltose vs. the ferric derisomaltose groups, 12 (20.0) vs 0 patients in trial A and 14 (24.6) vs 2 (3.2) in trial B experienced hypophosphatemia. The incidence of hypophosphatemia at any time from baseline to day 35 in ferric derisomaltose group compared with the ferric carboxymaltose group in trial A was 7.9% vs 75.0% [adjusted rate difference,–67.0% (95% CI, –77.4% to –51.5%)], P < .001 favouring ferric derisomaltose and in trial B was 8.1% vs 73.7% [adjusted rate difference, –65.8% (95% CI, –76.6% to –49.8%)], P < .001 favouring ferric derisomaltose.

Critical Appraisal

Internal Validity

Both trials A and B were open-label randomized clinical trials. Although the methods for randomization appeared appropriate, there were some imbalances in baseline characteristics such as sex, race and minor imbalances in ferritin and TSAT levels. These imbalances may have resulted from the small sample sizes of the included studies, which increases the risk that prognostic balance between groups may not have been achieved. The open label nature of the study may increase the risk of bias in determining the magnitude of the subjective safety outcomes. The efficacy outcomes are objective and unlikely to be at risk of bias on account of the open-label design. However, the changes from baseline and between-group differences with confidence intervals were not reported for some of the efficacy outcomes (Hb, Ferritin and TSAT) which precludes judgments about the precision of the effects. There was no adjustment for multiple comparisons which increases the risk of type 1 error (false positives) for statistically significant results. There was no imputation of missing values in this trial except for the change from baseline in patients with no postbaseline measurements which was set to zero at the first postbaseline visit. The risk of bias due to missing outcomes data is low considering the low rate of attrition in both trials.

External Validity

The included patients were mostly women with iron-deficiency anemia due to gynecological bleeding. In both trials, most of the patients were white, therefore, results may not be generalizable to a broader population. Although the outcome measures were appropriate, some outcomes that may be important to patients (e.g., HRQoL) were not reported. Patients with conditions such as alcohol or drug abuse, pregnancy or lactation, untreated hyperparathyroidism, kidney transplantation, body weight less than 50 kg, hemochromatosis or other iron-storage disorder were excluded, and the results are not generalizable to these group of patients. In this study, all patients in ferric carboxymaltose groups received 750 mg ferric carboxymaltose on days 0 and 7, whereas those in the ferric derisomaltose group had 1000 mg on day 0. According to the product monograph for ferric carboxymaltose a single dose should not exceed 15 mg iron/kg body weight or 1000 mg of iron. Based on Product monograph for ferric derisomaltose allowable iron dose per infusion is limited to 20 mg iron/kg body weight. While the dosage administered aligned with the product monographs, patients in the ferric carboxymaltose arm received 500 mg more iron vs the ferric derisomaltose arm. Because of the short follow up time, this study dose not inform long term clinical implications of these drugs. Additionally, the clinical outcomes associated with hypophosphatemia have not been reported.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adults (aged 18 years and older), adolescents (aged 14-17 years) and pediatric (aged 1-13 years) patients with IDA when oral iron preparations are not tolerated or are ineffective.
Treatment	Ferric carboxymaltose
Dose regime	The sponsor estimated an average cumulative iron dose (i.e. a treatment course) of 1,500 mg per adult, 1,119 mg per adolescent and 600 mg per pediatric patient (weight-based and dependent on Hb levels). A single ferric carboxymaltose administration should not exceed either 15 mg iron/kg body weight or 1000 mg iron for adults and should not exceed either 15 mg/kg or 750 mg iron for children and adolescents. If the total iron need (i.e. cumulative iron dose) is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.
Submitted price	Ferric carboxymaltose, 50 mg elemental iron per mL, intravenous $45.00 per 2 mL single-use vial $225.00 per 10 mL single-use vial $450.00 per 20 mL single-use vial
Submitted treatment costs	• Adults (18 years and older): $800 per treatment course[a] • Adolescents (aged 14-17 years): $665 per treatment course[a] • Pediatric (aged 1-13 years): $381 per treatment course[a]
Comparator(s)	• Ferric derisomaltose • Iron sucrose
Perspective	Canadian publicly funded health care payer
Time horizon	Single treatment course (i.e. one cumulative iron dose)
Key data source	FERGlcor and REPAIR-IDA open-labelled, randomized control trials comparing ferric carboxymaltose to iron sucrose, a 2017 published meta-analysis (comparing ferric carboxymaltose iron sucrose, ferric derisomaltose and oral iron in patients with IBD), and two published indirect treatment comparisons (Pollock and Muduma 2019; Han et al. 2023)
Costs considered	Drug acquisition costs, administration costs
Key limitations	• The sponsor's assumption of equivalent clinical efficacy and safety between ferric carboxymaltose and comparators is uncertain. In adults, ferric carboxymaltose demonstrated equivalent efficacy when compared to ferric derisomaltose or iron sucrose; although comparative evidence in pediatric and adolescent is lacking. Assumption of equivalent safety remains highly uncertain as there may be an increased risk of hypophosphatemia with ferric carboxymaltose. If hypophosphatemia is of clinical importance, a cost-utility analysis should have been submitted. Furthermore, the costs of managing adverse events, specifically treatment-emergent hypophosphatemia, were not included in the sponsors' analysis. • Variability exists in clinical practice on the approach to calculate total iron dose per treatment course and minimum infusion times that would impact the expected cost-savings derived from administration costs (nurse time, infusion chair time and infusion devices).
CDA-AMC reanalysis results	CDA-AMC did not undertake a base-case reanalysis. Given the higher rates of hypophosphatemia observed with ferric carboxymaltose, the extent of savings that will be realized with the use of ferric carboxymaltose compared to ID or ferric derisomaltose is highly uncertain. A scenario analysis including costs associated with monitoring and treating patients with non-severe hypophosphatemia estimated that cost-

Component	Description
	savings would be reduced. Reimbursement of ferric carboxymaltose may lead to additional costs to the health care system that have not been fully considered within this analysis.

Hb = hemoglobulin; IDA = iron deficiency anemia; IBD = inflammatory bowel disease; CKD = chronic kidney disease

[a] Treatment costs include costs of drug acquisition, nurse time, infusion chair time and infusion devices.

Budget Impact

CDA-AMC identified the several key limitations with the sponsor's analysis. The sponsor's use of a claims-based approach to estimate market size and market shares introduced uncertainty in the anticipated budget impact of ferric carboxymaltose. The market capture of ferric carboxymaltose was also uncertain. The sponsor's approach to including dispensing and mark-up fees was inappropriate and the submitted model was not user-friendly. Due to the limitations with the sponsor's claims-based analysis that could not be adequately validated or addressed, CDA-AMC did not conduct base case reanalyses. It should be noted that the sponsor's estimated incremental budget impact of $23,522,171 ($364,157 in the outpatient settings and $23,158,014 in the inpatient settings) over three years is highly uncertain.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: October 23, 2024

Regrets:

Two expert committee members did not attend.

Conflicts of interest:

None