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Reimbursement Recommendation

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

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Ferinject?

The Canada's Drug Agency (CDA-AMC) Canadian Drug Expert Committee (CDEC) recommends that public drug programs reimburse Ferinject for the treatment of iron deficiency anemia if certain conditions are met.

Which Patients Are Eligible for Coverage?

Ferinject should only be covered to treat patients with iron deficiency anemia who are aged 1 year or older when oral iron preparations are not tolerated or are ineffective according to the reimbursement criteria used for IV iron formulations that are currently reimbursed by public drug plans. CDEC noted 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.

What Are the Conditions for Reimbursement?

Ferinject should only be reimbursed if it is prescribed by a clinician with expertise in managing iron deficiency anemia in adult and pediatric patients aged 1 year and older and the cost of Ferinject is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 4 clinical trials showed that, in patients with iron deficiency anemia, treatment with Ferinject resulted in a similar clinical benefit as IV iron sucrose for improving hemoglobin levels, ferritin, and transferrin saturation levels.
- CDEC noted that, compared to IV iron sucrose, Ferinject provided a higher-dose iron formulation that required fewer infusions, which may offer enhanced convenience and improved quality of life.
- Based on the CDA-AMC assessment of the health economic evidence, Ferinject does not represent good value to the health care system at the public list price. The committee determined that uncertainty remains surrounding savings in administration costs and the assumption of comparative safety. A price reduction is therefore required.
- Based on public list prices, Ferinject is estimated to cost the public drug plans approximately $23.5 million over the next 3 years. However, the actual budget impact is uncertain.

Summary

Additional Information

What Is Iron Deficiency Anemia?

Anemia is a blood disorder that occurs when the blood lacks adequate healthy red blood cells to carry oxygen throughout the body. Iron deficiency anemia is due to insufficient iron to produce enough oxygen-carrying substance (hemoglobin) in red blood cells, enabling them to carry oxygen to the body's tissues. Symptoms of iron deficiency anemia include extreme fatigue, headache, shortness of breath, and muscle weakness. Anemia occurs in approximately 3% of Canadians, and iron deficiency is the most common cause of anemia.

Unmet Needs in Iron Deficiency Anemia

Iron deficiency anemia is treated with iron supplements, usually taken by mouth (orally). However, oral iron supplements may not suit patients who cannot tolerate or use them according to the correct instructions. Also, because oral iron takes time to produce the needed correction, it may not be suitable in patients with severe iron deficiency anemia. In such patients, iron may be given intravenously, or the patients may need blood transfusions to help replace iron and hemoglobin quickly.

How Much Does Ferinject Cost?

Treatment with Ferinject is expected to cost approximately $225 to $900 per adult (aged 18 years and older) and $90 to $675 per pediatric patient (aged 1 to 17 years) per the treatment course.

Recommendation

The Canada's Drug Agency (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 III, open-label, randomized controlled trials (RCTs) (VIT-IV-CL-015: N = 240; FERGIcor: N = 485) and 2 additional RCTs (1VIT05006: N = 559; VIT-IRON-2011-004: N = 371) demonstrated that treatment with ferric carboxymaltose resulted in a similar clinical benefit for patients with IDA compared with IV 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 IV iron sucrose, CDEC concluded that ferric carboxymaltose is 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 incur 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 because ferric derisomaltose allows for a higher maximum dose per single infusion. CDEC noted that if patients develop more severe adverse events (AEs) (e.g., severe hypophosphatemia, hypophosphatemia osteomalacia, and/or fractures), savings associated with the reimbursement of ferric carboxymaltose may be further reduced or eliminated, which was not 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	There is no evidence that ferric	CDEC agreed with the clinical experts'

Reimbursement condition	Reason	Implementation guidance
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.	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, in pregnant patients, the drug presents a high-dose option requiring fewer infusions compared to the currently used off-label iron sucrose.	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 than 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 than 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 compared to the total costs of other IV iron therapies. However, there remains uncertainty concerning the comparative safety across iron products and whether potential savings in administration costs compared to ferric derisomaltose will be realized in clinical practice.	—

Reimbursement condition	Reason	Implementation guidance
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.	—

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee.

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 IV 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 receive off-label treatment with other IV iron formulations, especially pregnant patients.
- **Indirect assessment of comparative clinical benefit:** CDEC discussed that although the sponsor-submitted direct evidence indicated that ferric carboxymaltose was at least as effective as iron sucrose or ferric derisomaltose in improving hemoglobin (Hb), 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 that 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 4 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 those 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 postmarketing period, some of which required 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, inflammatory bowel disease (IBD), and osteoporosis. The product monograph also recommended that serum phosphate levels be checked in patients at risk of low serum phosphate who require a repeat course of treatment within 3 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 and check-in). Clinical input indicates that both ferric derisomaltose and ferric carboxymaltose are likely to be administered similarly in practice — specifically, a maximum of 1,000 mg per single infusion and with identical infusion and observation times. Consequently, there are unlikely to be any significant differences in administration costs compared with ferric derisomaltose. If there are any potential cost-savings, these would entirely be driven by reduced administration costs. In such instances, such cost-savings would not be observed by public drug plan as such costs may pertain to a different budget holder.
- **AE costs:** CDEC noted that the sponsor did not incorporate AEs 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 AEs 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 AEs (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 Hb levels. Anemia has a range of causes; however, iron deficiency is the most prevalent. IDA results when body iron levels are insufficient to sustain Hb synthesis. The general Canadian population maintains a relatively low prevalence of anemia (approximately 3%). However, the prevalence is higher among Indigenous populations in Canada. A 2017 study of Inuit in Nunavik (aged 16 years and older) found that the prevalence of anemia was 20% in females 18 to 49 years of age, with 14% experiencing IDA and 23% demonstrating iron deficiency without anemia. Information for other groups of Indigenous Peoples was not available.

The key goals in treating iron deficiency 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 types of iron deficiency and IDA and is relatively safe, effective, and inexpensive. According to published recommendations, a switch to IV iron is proposed for severe anemia (Hb < 70 g/L) to avoid transfusion, for an underlying secondary disease fulfilling a formal indication for IV iron (e.g., IBD, chronic GI or genitourinary bleeding, celiac disease), and/

or for situations of nonadherence 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 IDA 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 millilitre containing 50 mg of elemental iron. The dosage of ferric carboxymaltose is expressed as milligrams of elemental iron, with each millilitre 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 1,000 mg of iron (20 mL ferric carboxymaltose) per week, and dosing follows a stepwise approach based on first, determination of the individual iron need; second, calculation and administration of the iron dose(s); and third, post iron repletion assessments.

The objective of this 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 IV infusion for the treatment of IDA in adult and pediatric patients aged 1 year 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 RCTs in patients with IDA due to various causes
  - 1 indirect treatment comparison
  - 7 additional studies addressing gaps in evidence
- patients' perspectives gathered by 1 patient group, the Gastrointestinal (GI) Society
- input from public drug plans that participate in the reimbursement review process
- 1 clinical specialist with expertise in diagnosing and treating patients with IDA
- a group of 12 clinicians, including those with specialties in cardiology, obstetrics and gynecology, hematology, gastroenterology, and nephrology, as well as 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 about 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 a significant impact on a patient physically, mentally, financially, and socially, and the extreme fatigue 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 because 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.
- According to the clinical expert, ferric carboxymaltose is most suitable for adults with iron deficiency or IDA, those unable to tolerate or respond to oral iron, and patients with IDA awaiting surgery. Ferric carboxymaltose is least suitable for patients with a history of hypophosphatemia. The clinical expert did not expect any issues with diagnosing IDA, with ferritin levels 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 iron deficiency 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; 12 weeks would be ideal.

Clinician Group Input

- A group of 12 clinicians, including those with specialties in cardiology, obstetrics and gynecology, hematology, gastroenterology, and nephrology, as well as a primary care physician provided 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 and/or 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 comparators
- 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 sponsor. There were no direct comparative studies in the submission comparing Ferinject to Monoferric. (Monoferric was also compared with iron sucrose.) Iron sodium ferric gluconate complex (Ferrlecit) 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, including 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 centres 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	
Definitions of IDA requiring IV iron can vary. For example, in Saskatchewan, the definition of IDA in adult patients is both of the following: • Hb less than 130 g/L • ferritin less than 30 mcg/L or TSAT less than 30% or blood loss greater than 1,000 mL within 7 days. The product monograph for Ferinject has dosing recommendations for patients with Hb greater than 140 g/L. Question for clinical expert: Are there specific laboratory parameter 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 IDA), the definition of IDA is Hb < 130 g/L (males) or < 120 g/L (females) AND ferritin < 30 mcg/L (although many clinicians will use ferritin < 50 mcg/L because there is evidence of normalized iron homeostasis when ferritin is > 50 mcg/L). Values for Hb also vary in pregnancy (first and third trimester: < 110 g/L; second 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 cut-offs for ferritin and TSAT based on specific conditions: • Inflammation — TSAT < 20% and ferritin < 100 mcg/L • CKD — TSAT < 30% and ferritin < 500 mcg/L

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 or 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 (refer to 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 (ferric derisomaltose or iron sucrose), 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 of those who should not receive Ferinject.
Oral iron is first line and inexpensive. Intolerance to oral iron can be difficult to determine and 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 an alternate day dosing regimen of oral iron • an adequate trial of at least 2 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? (e.g., bariatric surgery, IBD, CKD, short bowel?).	The clinical expert noted to CDEC the following: • Inadequate response to oral iron is failure to normalize iron stores by 3 months or failure to increment Hb by 10 g/L in 4 weeks. • 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 IDA (with 4 weeks or less to surgery), profound IDA (e.g., symptomatic anemia), active malignancy.
Patients receiving hemodialysis: 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 hemodialysis? Note: The indication for Monoferric is for patients who have non–hemodialysis-dependent CKD, and in patients receiving hemodialysis the shorter infusion time is not seen as a benefit as chair and nursing time are constant in this patient population. Note: The CDEC recommendation for Monoferric notes that it can be directly injected into the venous limb of a dialyzer.	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.
Monoferric would occupy a similar therapeutic space; Ferinject is indicated in pediatric patients and patients receiving hemodialysis. It also has a specific indication for iron deficiency associated with heart failure.	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 pediatric patients, both are used off-label in this patient population.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
IDA should be assessed and diagnosed through laboratory tests. The dose of Ferinject is determined through a combination of body weight and Hb level. Hb 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 500 mg to 2,000 mg depending on body weight and Hb level. The maximum dose is 1,000 mg per week; patients needing doses on the higher end (i.e., 2,000 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 every 3 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 after each administration.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Involvement of additional payers Proper management of IDA may lead to reduced requirement for blood products funded outside of the drug plan.	This is a comment from the drug programs to inform CDEC deliberations.
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.
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.
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.

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CHF = congestive heart failure; CKD = chronic kidney disease; Hb = hemoglobin; IBD = inflammatory bowel disease; IDA = iron deficiency anemia; NMA = network metanalysis; pCPA = pan-Canadian Pharmaceutical Alliance; TSAT = transferrin saturation.

Clinical Evidence

Pivotal Studies and Select RCTs

Description of Studies

The systematic review portion of this report focused on 4 studies: 2 pivotal phase III RCTs per the Health Canada review (VIT-IV-CL-015 and FERGIcor) and 2 phase III 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 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 noninferiority 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 the FERGIcor study, the mean age was 52.7 years (standard deviation [SD] = 13.8 years) in the ferric carboxymaltose group and 51.0 years (SD = 12.6 years) in the iron sucrose group, while in VIT-IV-CL-015 and in the other studies the mean age was approximately 40 years. In the VIT-IV-CL-015 study, approximately 42% of patients were female and 58% were male, and in FERGIcor 59% were female and 41% were male. In the nonpivotal trials that enrolled patients with IDA due to various causes, approximately 90% of all patients were female and 10% were male. Overall, mean Hb levels were 93.2 g/L in the VIT-IV-CL-015 study, 102.2 g/dL in the FERGIcor study, [redacted] g/L in the 1VIT05006 study, and less than 80 g/L in the VIT-IRON-2011-004 study.

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 the VIT-IV-CL-015 study, the primary response rate was defined as the percentage of patients reaching an increase in Hb of at least 10 g/L at 4 weeks after baseline. The percentage of patients who responded in the ferric carboxymaltose group was 45 of 97 (46.4%) and in the iron sucrose group 32 of 86 (37.2%) with a reported P value for the between-group difference of 0.2101. The mean increase of Hb at week 4 was [redacted] in the ferric carboxymaltose group and [redacted] in the iron sucrose group with a reported P value for the between-group difference of [redacted]. No between-group difference with a confidence interval (CI) was reported for either end point.

In the FERGIcor study, the primary outcome was Hb response of at least 20 g/L increase in Hb at week 12. In the full analysis set, 65.79% (150 of 240) in the ferric carboxymaltose group and 53.64% (118 of 220) in the iron sucrose group achieved Hb response. The between-group difference was 12.15% (95% CI, 3.07%

to 20.97%; P = 0.004). The full analysis 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 the VIT-IRON-2011-004 study, 99.5% (184 of 185) of patients in the ferric carboxymaltose and 98.3% (177 of 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 noninferiority were met. From a mean baseline of 77.4 g/L (SD = 14.95 g/L) in the ferric carboxymaltose group and 80.5 g/L (SD = 14.45 g/L) 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 the FERGIcor study, for the physical component of the Short Form (36) Health Survey (SF-36), from a mean baseline of 44.17 (SD = 7.36) in the ferric carboxymaltose group and 44.98 (SD = 7.23) in the iron sucrose group, there was a change from baseline to week 12 of 3.88 (SD = 6.77) and 2.64 (SD = 7.14), respectively, for a reported between-group P value of 0.157. For the mental component of the SF-36, from a mean baseline of 40.02 (SD = 11.04) in the ferric carboxymaltose group and 41.30 (SD = 11.70) in the iron sucrose group, there was a change from baseline to week 12 of 5.91 (SD = 10.74) and 5.56 (SD = 10.36), respectively, for a between-group P value of 0.583. For the Inflammatory Bowel Disease Questionnaire total score, from a mean baseline of 150.8 (SD = 35.2) in the ferric carboxymaltose group and 152.7 (SD = 34.4) in the iron sucrose group, there was a change from baseline to week 12 of 21.1 (SD = 32.3) and 19.7 (SD = 28.8), respectively, for a between-group P value of 0.872. Between-group differences with CIs were not reported for any of the health-related quality of life (HRQoL) measures.

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

Serum Ferritin

In the VIT-IV-CL-015 study, 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 CI was not reported.

In the FERGIcor study, 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 the VIT-IRON-2011-004 study, 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]

[redacted] in the iron sucrose group, for a least squares mean between groups of [redacted].

Transferrin Saturation

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

In the FERGIcor study, 117 of 222 patients (52.7%) in the ferric carboxymaltose group and 76 of 209 patients (36.4%) in the iron sucrose group had normal TSAT levels (20% to 50%) at week 12. The odds ratio was 2.05 (95% CI, 1.37 to 3.06; P < 0.001), in favour of ferric carboxymaltose. The absolute between-group difference with CI was not reported.

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

Patients Without Anemia

The percentage of patients without anemia at week 12 in the FERGIcor trial (Hb level ≥ 120 g/L for females or ≥ 130 g/L for males) was 72.8% (166 of 228) in the ferric carboxymaltose group and 61.8% (136 of 220) in the iron sucrose group. The odds ratio was 1.65 (95% CI, 1.10 to 2.46; P = 0.015). The absolute between-group difference with CI 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 1 AE. In the FERGIcor study, 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 1 AE. In the VIT-IRON-2011-004 study, there were [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group who had an AE.

Serious Adverse Events

In the VIT-IV-CL-015 study, serious AEs (SAEs) were reported in [redacted] patients in the ferric carboxymaltose group and || [redacted] patients in the iron sucrose group. In the FERGIcor study, there were SAEs in [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group.

In the 1VIT05006 study, [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the placebo group had an SAE. In the VIT-IRON-2011-004 study, [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 the VIT-IV-CL-015 study, [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the iron sucrose group withdrew from study medication due to AEs. In the FERGIcor study, 7 patients (2.9%) in the ferric carboxymaltose group and 2 patients (0.8%) in the iron sucrose group withdrew from the study drug due to an AE.

In the 1VIT05006 study, [redacted] patient in the ferric carboxymaltose group and |patients in the placebo group withdrew from study medication due to an AE. In the VIT-IRON-2011-004 study, |[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 the VIT-IV-CL-015 study due to acute anterior myocardial infarction. [redacted] died more than a week after study medication was withdrawn due to a nonserious AE. In the 1VIT05006 study, [redacted] patient in the ferric carboxymaltose group died due to pneumonia. There were no deaths reported in the other 2 studies.

Notable Harms

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

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

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 3 studies did not plan for any formal comparisons between ferric carboxymaltose and iron sucrose, while the other 2 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 with the iron sucrose group who withdrew from the VIT-IV-CL-015 study ([redacted]), and this may also bias assessment of efficacy and harms in this relatively short (4 weeks) study. Between-group differences with CIs 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 living in Canada who are Indigenous. With respect to outcomes, while 1 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 Grading of Recommendations, Assessment, Development, and Evaluations (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 IV iron therapies in the context of adults with IDA associated with IBD.

Description of Studies

The NMA submitted by the sponsor included 5 RCTs. All studies included patients with IBD. 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 sponsor was insufficient to determine whether there is a difference in efficacy or harms for ferric carboxymaltose compared with other injectable forms of iron in patients with IDA and IBD.

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, more than 8 years before the writing of 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 1 or 2 studies connecting the nodes and wide CrIs. Only 1 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 sponsor's lack of clear, a priori criteria for selecting the NMA. There are at least 2 other published NMAs investigating the relative efficacy of ferric carboxymaltose in broader patient populations with IDA. There was no protocol outlining a priori how 1 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 sponsor was insufficient to determine whether there is a difference in efficacy for ferric carboxymaltose compared with other injectable forms of iron in patients with IDA and IBD. 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 squares mean change in Hb from baseline to day 35 obtained through the analysis of covariance (ANCOVA) model was 2.22 g/dL [redacted] in the ferric carboxymaltose group 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 g/dL to 0.88 g/dL; P value = 0.3108). The results of the mixed model repeated measures (MMRM) model and the subgroup analyses align with the main analysis. The least squares mean change in ferritin from baseline to day 35 obtained through the ANCOVA model was [redacted] in the ferric carboxymaltose group and [redacted] in the oral iron group. The treatment difference at day 35 was [redacted]. The least squares mean change in TSAT levels from baseline to day 35 obtained through the ANCOVA model was [redacted] in the ferric carboxymaltose group 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 1 treatment-emergent AE (TEAE) [redacted] versus [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 the oral iron arm. There were also baseline imbalances by ethnicity and by body mass index. 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 which treatment they were assigned to (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 intention-to-treat (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 I error (false positives) for statistically significant results. Although the subgroup analyses were preplanned, these were unlikely powered to detect subgroup differences.

External Validity

The included patients are from the age group of 1 to 17 years, 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. Because 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, multicentre, randomized, active-controlled, open-label study to investigate the efficacy and safety of IV 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 (SOC) 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 SOC. 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 Hb from baseline to the highest value between baseline and day 35 or time of intervention 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 CI was reported. In a post hoc comparison of group C (ferric carboxymaltose) versus group D (IV SOC) (cohort 2), the mean increase in Hb from baseline to the highest value between baseline and day 35 or time of intervention was 2.90 g/dL [redacted] in group C (ferric carboxymaltose) and 2.16 [redacted] group D (IV SOC). No between-group difference with CI was reported. Subgroup analysis revealed the mean increase in Hb 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 Hb value or etiology of IDA.

In cohort 1, the proportion of patients achieving Hb greater than 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 greater than 12 g/dL and ferritin increase of 160 ng/mL or more 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 CIs were not reported for any outcome.

In cohort 2, the proportion of patients achieving Hb greater than 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 greater than 12 g/dL and ferritin increase of 160 ng/mL or more 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 CIs 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 SOC) ([redacted] across groups). The most commonly (≥ 5%) experienced TEAE in group A was nausea ([redacted]%),hypophosphatemia ([redacted]%) in group C, and dizziness ([redacted]%) in group D. No TEAE was experienced in 5% or more of patients in group B. [redacted] ([redacted]%) patients in group A (ferric carboxymaltose), [redacted] patients 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 AE 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 patients in the ferric carboxymaltose group were either grade 2 or 3, and in the IV SOC arm were grades 1 to 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 (erythema, 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] [redacted] in group B (oral iron), respectively. In group C (ferric carboxymaltose), [redacted] of patients experienced hypophosphatemia and [redacted] experienced PCS low phosphorus compared with [redacted] in group D (IV SOC), 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 || grade || 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 white blood cell count on days when phosphorus was grade 4. In total, | | deaths were reported in the study: ||| in group B (oral iron), | | 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 SOC). It is uncertain 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 which treatment they were assigned to (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 handling 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 modified ITT (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 I error (false positives) for statistically significant results. Between-group differences with CIs were not reported for any outcome, precluding judgments about the precision of the effects.

External Validity

In this study, all patients received 2 doses of 15 mg iron per kilogram, up to a maximum single dose of 750 mg iron and a maximum cumulative dose of 1,500 mg iron. These values were aligned with recommended dosing in the product monograph, which recommends a maximum single relative dose of 15 mg iron per

kilogram, a maximum single absolute dose of 1,000 mg, and a maximum total dose of 2,000 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 was conducted in 84 US centres only, with no patients from Canada and no representation of Indigenous Peoples, who are disproportionately affected by IDA. Because 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 ( ) were not enrolled. As such, the enrolled patients may not be representative of patients seen in clinical practice (because 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 et al. (2023)

The study by Zoller et al. (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), levels 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 g/L to 28.8 g/L) and in the ferric carboxymaltose group was 25.2 g/L (95% CI, 21.3 g/L to 29.1 g/L). The between-group difference with CI was not reported for any efficacy outcome. Both ferric derisomaltose and ferric carboxymaltose resulted in improvement in fatigue symptoms and increased Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) scores, which was statistically significantly greater for patients treated with ferric derisomaltose versus ferric carboxymaltose at days 35 and 49. The between-group difference with CI 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% versus 2.1% and vitamin D deficiency: 34.7% versus 22.9%, respectively). Numerically, fewer patients experienced headache and nausea in the ferric carboxymaltose group compared with the ferric derisomaltose group (headache: 10.2% versus 18.8% and nausea: 2.0% versus 12.5%, respectively). Discontinuation due to AEs occurred among 6.3% of patients in the 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 a serum phosphate level of less than 2.0 mg/dL. The primary end point was the incidence of hypophosphatemia at any time after the first dose to day 35, which was reported in 8.3% (4 of 48) of patients in the ferric derisomaltose group and 51.0% (25 of 49) of patients in the ferric carboxymaltose group with an 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 hypophosphatasemia 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 disease, respectively (interaction P value = 0.1948). The highest incidence of hypophosphatemia occurred within 2 weeks of treatment in both arms. The secondary safety end point was the incidence of hypophosphatemia at any time from baseline to day 70, which occurred among 12.5% (6 of 48) of patients in the ferric derisomaltose group and 59.2% (29 of 49) of patients 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 with ferric derisomaltose infusion (between-group differences with CIs were not reported). For more than 1 month after the second infusion, 4.7% (2 of 43) of patients in the ferric carboxymaltose group remained hypophosphatemic. On day 70, the mean serum phosphate remained significantly lower in the ferric carboxymaltose group compared with the ferric derisomaltose group (between-group differences with CIs were not reported).

Critical Appraisal

Internal Validity

Although the methods for randomization appeared appropriate, there is an increased risk that prognostic balance was not achieved due to the small sample size, as evidenced by imbalances in some baseline disease and demographic characteristics. Notably, there were imbalances at baseline in IBD diagnosis (Crohn 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 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 a low risk of bias in the measurement of the outcomes. Considering the importance of patient-reported outcomes, the use of FACIT-Fatigue, which is a reliable and valid instrument for measuring fatigue in IBD, was appropriate. Because the trial was double-blinded, the risk of bias due to reporting subjective patient-reported outcomes is low. However, because the between-group difference with CI was not reported at any follow-up time point, this 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. The proportion of patients with missing data was low for this outcome; therefore, there is likely low risk of bias due to missing outcomes data. Further, a post hoc sensitivity analysis, in which these patients were imputed as either being free of hypophosphatemia or 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 the ferric derisomaltose group and 12.5% in the 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. Between-group

differences with CIs were not reported, particularly for efficacy outcomes (e.g., change in Hb, ferritin, TSAT, and fatigue), precluding conclusions about the magnitude (including clinical importance) of the estimated effects and their precision.

External Validity

The results may not be broadly generalizable because of the small sample size of the trial. 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, conclusions about the magnitude of the estimated effects and their precision were limited due to insufficient reporting of between-group differences and CIs. Indigenous Peoples, who are disproportionately affected by IDA, were not represented in this study. In this trial, patients received a single IV infusion of 1,000 mg of either ferric derisomaltose or ferric carboxymaltose at baseline (day 0) and, depending on the a priori calculated iron dose, if needed, either 500 mg or 1,000 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 1,000 mg of iron. Based on the product monograph for ferric derisomaltose, the allowable iron dose per infusion is limited to 20 mg iron/kg body weight. The dosage administered in this trial aligns with the product monographs.

Emrich et al. (2020)

The study by Emrich et al. (2020) is a prospective, single-centre, double-blind study. The study randomized 26 women with IDA to receive ferric carboxymaltose (n = 13 patients) or ferric derisomaltose (n = 13 patients). This trial aimed to assess hypophosphatemia after high-dose iron repletion with ferric carboxymaltose and ferric derisomaltose. Change in the levels of Hb, ferritin, and TSAT were not among the trial end points and were not reported. The primary outcome was hypophosphatemia at any postinfusion 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% (3 of 12) and 8% (1 of 13) of patients in the ferric carboxymaltose and ferric derisomaltose groups, respectively, had hypophosphatemia. The between-group difference with CI 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 that might be due to the small sample size. Further, due to logistic reasons, after the inclusion of 26 patients (instead of the 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, the effect size may have differed. Due to lack of information in the publication, the adequacy of blinding is unclear. Only 1 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 because statistical analyses were not adjusted for multiple comparisons. The between-group differences with CIs 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” [from original source] the results may not be broadly generalizable. Further, the results are also not generalizable to 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” [from original source], or a 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 1 infusion was performed which limits detection of consequences of repeated infusions.

Wolf et al. (2020)

Wolf et al. (2020) reports on 2 identically designed, open-label, randomized clinical trials that 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 levels from trial A and B were reported; however, changes from baseline and between-group differences with CIs were not reported for Hb, ferritin, and TSAT outcomes at any time point.

Overall, in the ferric carboxymaltose versus the ferric derisomaltose groups, 27 of 60 (45.0%) patients versus 7 of 63 (11.1%) patients in trial A and 28 of 57 (49.1%) versus 14 of 62 (22.6%) patients in trial B experienced AEs. 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 versus the ferric derisomaltose groups, 12 (20.0%) patients versus 0 patients in trial A and 7 (12.3%) patients versus 0 patients in trial B experienced decreased blood phosphorus. In the ferric carboxymaltose versus the ferric derisomaltose groups, 12 (20.0%) patients versus 0 patients in trial A and 14 (24.6%) patients versus 2 (3.2%) in trial B experienced hypophosphatemia. The incidence of hypophosphatemia at any time from baseline to day 35 in the ferric derisomaltose group compared with the ferric carboxymaltose group in trial A was 7.9% versus 75.0% (adjusted rate difference = –67.0%; 95% CI, –77.4% to –51.5%; P < 0.001 favouring ferric derisomaltose) and in trial B was 8.1% versus 73.7% (adjusted rate difference = –65.8%; 95% CI, –76.6% to –49.8%; P < 0.001 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 and 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 because of the open-label design. However, the changes from baseline and between-group differences with CIs 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 I 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 patients included in the study were primarily females with IDA 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 misuse of alcohol or drugs, pregnancy or lactation, untreated hyperparathyroidism, kidney transplantation, body weight less than 50 kg, hemochromatosis, or another iron storage disorder were excluded, and the results are not generalizable to these group of patients. In this study, all patients in the ferric carboxymaltose groups received 750 mg ferric carboxymaltose on days 0 and 7, whereas those in the ferric derisomaltose group received 1,000 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 1,000 mg of iron. Based on the product monograph for ferric derisomaltose, the 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 than those in the ferric derisomaltose arm. Because of the short follow-up time, this study does 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

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adults (aged 18 years and older), adolescents (aged 14 to 17 years), and pediatric (aged 1 to 13 years) patients with IDA when oral iron preparations are not tolerated or are ineffective.
Treatment	Ferric carboxymaltose

Component	Description
Dose regimen	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 1,000 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, IV • $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 to 17 years): $665 per treatment course[a] • Pediatrics (aged 1 to 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., 1 cumulative iron dose)
Key data source	Equivalent clinical efficacy was assumed based on the open-label, randomized controlled trials, FERGIcor and REPAIR-IDA, a 2017 published meta-analysis and 2 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 with ferric derisomaltose or iron sucrose, although comparative evidence in pediatrics and adolescents is lacking. Assumption of equivalent safety remains highly uncertain because 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, which 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 iron sucrose or ferric derisomaltose is highly uncertain. A scenario analysis including costs associated with monitoring and treating patients with nonsevere hypophosphatemia estimated that cost-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.

CDA-AMC = Canada's Drug Agency; Hb = hemoglobulin; IBD = inflammatory bowel disease; IDA = iron deficiency anemia.

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

Budget Impact

CDA-AMC identified 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 setting and $23,158,014 in the inpatient setting) over 3 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

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.