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 in adult patients with heart failure and NYHA class II/III to improve exercise capacity.

Sponsor: CSL Vifor

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: March 2025
Report Length: 31 Pages

Single Technology

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that ferric carboxymaltose be reimbursed for the treatment of iron deficiency (ID) in adult patients with heart failure and New York Heart Association (NYHA) class II/III to improve exercise capacity only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 3 studies (FAIR-HF [N = 459], CONFIRM-HF [N = 304], and HEART-FID [N = 3065]) in patients with chronic heart failure (CHF), demonstrated that treatment with ferric carboxymaltose likely results in an improvement in NYHA class at 24 and 52 weeks, Kansas City Cardiomyopathy Questionnaire (KCCQ) at 52 weeks, fatigue score at 24 and 52 weeks, and serum ferritin at 24 and 52 weeks. However, CDEC noted that there is uncertainty regarding whether the magnitude of benefit is clinically meaningful for all of the aforementioned outcomes. In addition, treatment with ferric carboxymaltose in patients with CHF may also result in an improvement in KCCQ at 24 weeks but the certainty was lower at this time-point due to imprecision. Regarding the effect of ferric carboxymaltose on 6-minute walk test (6MWT) in patients with CHF at 24 or 52 weeks, the evidence was very uncertain due to inconsistency, imprecision, and missing data. Notably, FAIR-HF and CONFIRM-HF studies showed likely clinically meaningful improvement when compared with placebo, while HEART-FID did not show an improvement in the 6MWT when compared with placebo. The reason for this discrepancy is not fully clear. Finally, ferric carboxymaltose may result in little-to-no difference in cardiovascular (CV) mortality when compared to placebo at 26 or 52 weeks, but the duration of follow-up may be inadequate and studies may be inadequately powered to fully assess this outcome. Finally, 1 study (AFFIRM-AHF [N = 1132]) that assessed efficacy and safety of ferric carboxymaltose in patients with acute heart failure (AHF) was also reviewed, however, this study did not assess the impact of ferric carboxymaltose on exercise capacity. CDEC noted that the results from the Ponikowski et al. meta-analysis which utilized individual patient data from CONFIRM HF, HEART-FID and AFFIRM-AHF demonstrated that compared to placebo, patients treated with Ferric carboxymaltose experienced reduction in total hospitalizations, total heart failure (HF) hospitalizations, and the composite outcome of total CV hospitalization and CV death.

The clinician group input received, and the clinical expert consulted for this review noted that for patients with heart failure (HF), iron deficiency (ID) exacerbates symptoms, accelerates disease progression, and worsens prognosis, and that ID is also associated with reduced functional capacity, more frequent hospitalizations, and higher mortality rates. It was also noted that the main treatment goals are to address low hemoglobin levels, replenish iron stores, and maintain them over time to alleviate symptoms, improve health-related quality of life (HRQOL), and enhance functional and exercise capacity. CDEC noted that while ferric carboxymaltose might increase serum ferritin levels, it is uncertain whether it will have an impact on functional and exercise capacity, HRQoL, and cardiovascular mortality. Therefore, it is uncertain whether ferric carboxymaltose addresses some of the unmet needs identified for this patient population such as improving exercise capacity, HRQoL, and cardiovascular mortality.

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. Adult patients with heart failure and NYHA class II or III who have HF and who have all the following: 1.1. Have LVEF ≤ 40% 1.2. Have ferritin ≤ 300 µg/L with a TSAT < 15%	The majority of patients included the in Ponikowski et al. meta-analysis had NYHA class II to III and LVEF ≤ 40% Ponikowski et al. meta-analysis found a significant interaction between TSAT levels and the composite outcome of CV hospitalization and CV death (interaction P = 0.019), as well as for CV death alone (interaction P = 0.035) and that patients in the lowest TSAT tertile (<15%) experienced a greater treatment effect compared to those with higher baseline TSAT levels.	
2. Duration of initial authorization is 24 weeks	FAIR-HF and CONFIRM-HF are the two trials showing potentially clinically meaningful 6MWT at 24 weeks and NYHA.	—
Renewal		
3. For renewal after initial authorization and each subsequent annual renewal, the physician must provide proof that the criteria in condition 1 above still applies.	Ensure patients are still in need of treatment with ferric carboxymaltose.	—
Prescribing		
4. Cardiologist or clinician experienced in the management of chronic HF	This is meant to ensure that ferric carboxymaltose is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner	—
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 the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

CV = cardiovascular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TSAT = transferrin saturation

Discussion Points

- **Reconsideration request:** the sponsor requested a reconsideration of the initial CDEC draft recommendation to not reimburse ferric carboxymaltose for the treatment of ID in adult patients with heart failure and New York Heart Association (NYHA) class II/III to improve exercise capacity. CDEC discussed three issues outlined by the sponsor in the request for reconsideration. In the first issue the sponsor requested that CDEC consider additional context when interpreting the HEART-FID results, in the second issue the sponsor was of the view that the there is evidence that indicate that ferric carboxymaltose would reduce hospitalization in patients with ID and HF, in the third issue the sponsor indicated that there is an unmet need in patients with HF.

- **Treatment goals:** During the initial meeting and reconsideration meeting,CDEC discussed that when iron levels are too low to support adequate hemoglobin synthesis it can impairs the blood's ability to carry oxygen efficiently either due to a reduced number of red blood cells or low hemoglobin (Hb) levels. In patients with HF and ID, iron correction is theorized to improve HRQoL, functional capacity, and exercise capacity and alleviate symptoms associated with ID. The clinical expert noted to CDEC that the treatment goal of IV iron is not necessarily to improve hospitalization and mortality directly as these are likely more strongly driven by the patient's underlying HF, which is not modified by iron supplementation.

- **GRADE assessment:** CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the included studies for patients with CHF concluded with moderate certainty that treatment with ferric carboxymaltose likely results in an improvement in NYHA class, fatigue score, serum ferritin, and hospitalization when compared with placebo, however, it was noted that there is uncertainty regarding whether the magnitude of benefit is clinically meaningful for these outcomes. Assessment of exercise capacity using 6MWT was not conclusive and did not show a clearly meaningful benefit of ferric carboxymaltose over placebo, and GRADE assessment of evidence was of very low certainty.

- **Uncertainty in the evidence with regards to exercise capacity:** CDEC discussed the uncertainty in the results for 6MWT which was mainly driven by the inconsistency between the studies and that confidence intervals (CIs) and some effect estimates included potential for both clinically meaningful benefit and little to no benefit. CDEC noted that the largest study, HEART-FID, is also the most recent and enrolled patients with similar characteristics to patients with HF who live in Canada with regards to geographical location of the sites; this study also found the least apparent benefit in 6MWT, and its 95% CIs did not or minimally overlapped with those of the other studies contributing data to this outcome, and that there were also some concerns about missing data.

- **Evidence in AHF:** CDEC discussed the results of the AFFIRM-AHF study, which enrolled patients with acute heart failure (AHF). The study showed that ferric carboxymaltose likely results in improvements in NYHA class, KCCQ score, serum ferritin levels, and cardiovascular hospitalization rates. However, CDEC noted that there was uncertainty about whether the observed effects were clinically significant for all the mentioned outcomes. Additionally, there was a lack of data regarding the impact of ferric carboxymaltose on exercise capacity or fatigue in patients with AHF.

- **Comparators:** During the initial meeting and reconsideration meeting, CDEC discussed that other intravenous (IV) formulations of iron supplementation exist and are used off-label in clinical practice to treat patients with HF; however, no

direct or indirect evidence comparing ferric carboxymaltose to other IV irons is available. Therefore, no conclusions can be drawn regarding the relative efficacy and safety of ferric carboxymaltose compared to other commonly used IV iron formulations in patients with HF. During the reconsideration meeting, CDEC noted that although access of IV iron may vary across jurisdictions, it would appear patients with HF and ID do receive IV iron. Evidence to address an unmet need related to differences to infusion time was not provided nor any comparative evidence.

- **Cardiovascular outcomes:** during the reconsideration meeting, CDEC discussed the results from Ponikowski et al. meta-analysis which utilized individual patient data from CONFIRM HF, HEART-FID and AFFIRM-AHF. CDEC noted that the results appear clinically important, demonstrating that compared to placebo, patients treated with Ferric carboxymaltose experienced reduction in the composite outcome of total CV hospitalization and CV death, total hospitalizations, and total HF hospitalizations. However, it was noted that the meta-analysis did not show a reduction in time to CV death or time to all-cause death, nor did it report on HRQoL outcomes or exercise capacity (e.g., 6- MWT). CDEC also discussed that Ponikowski et al. meta-analysis explored the outcomes related to baseline TSAT and it was reported that those with TSAT <15% was the only group that resulted in reduction in the composite outcome of total CV hospitalizations and CV death while those with baseline TSAT between 15 and 24% and TSAT at least 24% did not appear to derive statistically significant benefit from FCM therapy. The same trends were observed for the composite outcome of total HF hospitalization and CV death.

- **Hypophosphatemia risk:** during the reconsideration meeting, CDEC noted that Ferric carboxymaltose is associated with a risk of hypophosphatemia, as detailed in the product monograph, which is not the case to the same magnitude among the other IV iron formulations. Events of hypophosphatemia were rare in the included studies, where reported, but there are concerns about the reporting given that events (including several severe events) do appear to have occurred without being recorded as TEAEs in CONFIRM-HF. It is unknown whether similar events occurred in the other trials and were unreported. Discussion with clinical experts consulted in the ferric carboxymaltose review pertaining to patients with IDA (outside of the HF context) elucidated that hypophosphatemia is relatively easy to manage with inexpensive oral supplements, although it may incur additional monitoring costs, and untreated hypophosphatemia can result in serious health risks. CDEC also noted that 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:** during the reconsideration meeting, CDEC discussed that 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 variability in clinical practice on how the cumulative iron dose is determined and administered across ferric carboxymaltose indications. 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:** during the reconsideration meeting, 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.

- **Budget Impact is highly uncertain:** during the reconsideration meeting, CDEC notes that the sponsor's estimates for the budget impact were based on historical volume of claims. It is unclear whether these claims included the treatment of ID for patients with HF, or if they only represented patients with HF that also already met reimbursement criteria for the treatment if IDA. Since FCM is explicitly indicated for the treatment if ID (not necessarily accompanied by IDA) the number of patients with HF that will meet criteria is potentially much larger than the number of historical claims. Hence, the true budget impact is unknow.

Background

Heart failure (HF) is a complex and life-threatening syndrome in which abnormal heart function leads to subsequent risk of clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress. This condition is marked by significant morbidity and mortality, reduced functional capacity and poor quality of life. Patients with chronic heart failure (CHF) require continuous medical care, frequent monitoring, hospitalizations, and extensive treatment. Symptoms of HF are classified using the New York Heart Association (NYHA) functional classes I to IV, which categorize the severity of symptoms ranging from minimal limitations during physical activity (Class I) to severe symptoms even at rest (Class IV). These symptoms reflect the progressive impact of HF on daily activities and quality of life. Approximately 60% of patients with HF have anemia and 40% of those without anemia have iron deficiency (ID). When iron levels are too low to support adequate hemoglobin synthesis, it can lead to iron deficiency anemia (IDA), which impairs the blood's ability to carry oxygen efficiently either due to a reduced number of red blood cells or low hemoglobin (Hb) levels. While anemia can have various causes, iron deficiency is the most prevalent. This condition significantly impacts patient well-being and outcomes as iron plays a critical role in oxygen transport and cellular energy metabolism, particularly in high-energy-demanding tissues like cardiac muscle. The prevalence of ID is 35 to 55% in HF outpatients and 72 to 83% in patients admitted to hospital due to HF. A recent study in Alberta found that among 17,463 patients with acute HF (AHF), 38.5% had their iron status evaluated within 30 days post-index episode, compared to 34.2% of 11,320 patients with CHF. Of those tested, 72.6% and 73.9% of patients with acute and chronic HF, respectively, were found to have ID.

Ferric carboxymaltose is a colloidal dispersion which contains iron in a stable ferric state. This complex consists of a polynuclear iron-hydroxide core bound to a carbohydrate ligand. It is specifically formulated to provide easily utilizable iron for the body's iron transport and storage proteins, namely transferrin and ferritin. Ferric carboxymaltose was approved by Health Canada For the treatment of ID in adult patients with heart failure and NYHA class II/III to improve exercise capacity. The diagnosis of ID must be based on laboratory tests. The dosage of ferric carboxymaltose is expressed as mg of elemental iron, with each mL containing 50 mg of elemental iron. The recommended dosing of ferric carboxymaltose for adult patients follows a stepwise approach by first determining the individual iron need for repletion based on the patient’s body weight and hemoglobin (Hb) level. The maximum recommended cumulative dose of ferric carboxymaltose is 1000 mg of iron (20 mL ferric carboxymaltose) per week.

Sources of Information Used by the Committee

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

- a review of four placebo-controlled, double-blind, randomized trials, 3 of which enrolled patients with CHF (FAIR-HF, CONFIRM-HF, and HEART-FID), and 1 enrolled patients with AHF (AFFIRM-AHF).
- input from public drug programs that participate in the reimbursement review process
- One clinical specialist with expertise diagnosing and treating patients with heart failure
- input from one clinician group, a group of 13 independent clinical experts
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor’s request for reconsideration (described subsequently)
- feedback on the draft recommendation

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

No patient group input was submitted.

Clinician Input

Input From Clinical Experts Consulted for This Review

Treatment of ID with oral iron, although widely available and inexpensive, was described by the expert to be of limited utility due to poor absorption in general, but especially amongst patients with HF due to a variety of physiological factors specific to HF, such as epithelial dysfunction in the gut because of mucosal edema and reduced intestinal blood flow. The clinical expert indicated that intravenous (IV) iron is currently the preferred and guideline-recommended route for treatment of ID in patients with HF, and the intention of iron supplementation for ID in patients with HF is to improve HRQoL, functional capacity, and exercise capacity. The clinical expert described that IV irons typically used in clinical practice include iron sucrose (maximum dose of 200 mg per sitting), ferric derisomaltase (maximum dose of 1000 mg per injection), or ferric carboxymaltose (maximum dose of 1000 mg per week). Of the IV iron formulations, only ferric carboxymaltose has a Health Canada approved indication specific to the HF subpopulation, however the other second- or third-generation IV irons may also be used in clinical practice in this population.

The expert noted that guidelines for the treatment of HF recommend all patients with HF should be tested for ID using serum ferritin and TSAT, and Canadian treatment guidelines recommend consideration of IV iron therapy for HF patients with all of the following: left ventricular ejection faction ≤ 40%, serum ferritin < 100 µg/L or between 100 to 299 µg/L with transferrin saturation < 20%. The expert noted that based on Canadian and multiple international treatment guidelines for patients with HF and ID, patients with HF of any NYHA class may potentially be suitable for treatment with IV iron formulations, including ferric carboxymaltose.

The clinical expert noted that most patients with HF receiving IV iron supplementation would be expected to continue this therapy for the duration of their lives. So long as guideline criteria for iron replacement therapy maintain, and aside from intolerable AE or patient or clinician decision or preference, there are no specific reasons to require discontinuation of ferric carboxymaltose in a patient with HF and ID. According to the expert, there was no threshold of any laboratory parameter under which the drug should be discontinued due to lack of efficacy, and treatment should be required for as long as dictated by guideline criteria for ID-related IV iron replacement therapy.

IV iron formulations such as ferric carboxymaltose are prescribed in hospital and can be prescribed by any prescribing clinician managing the patient's HF and ID in that setting.

Clinician Group Input

A group of 13 independent clinical experts responding to CDA-AMC's call gathered data from product monographs, literature, and personal experience. According to the group, ID is a progressive condition that can lead to IDA if untreated, affecting and impacting patients with HF by worsening disease symptoms and prognosis.

The clinician group emphasized that treatment goals include correcting hemoglobin deficits, replenishing iron stores, and maintaining them over time to alleviate symptoms and enhance health-related quality of life. While initial therapy often involves oral iron supplements, IV iron is recommended as the first-line treatment for patients with HF due to its rapid efficacy, especially since up to 50% of HF patients can experience ID, leading to poorer functional capacity and increased hospitalizations and mortality. The clinician group noted that guidelines advocate for initiating IV iron therapy as soon as ID is identified.

The group noted challenges with previous IV iron formulations in Canada, requiring prolonged administration and none were indicated for use in pediatric populations or for the treatment of patients with ID and HF, underscoring the need for more efficient options. Newer products like ferric carboxymaltose can deliver high doses (up to 1000 mg) in a single session, potentially reducing treatment burden and improving adherence.

The clinician group indicated that treatment response is assessed using hematologic and iron parameters, aiming to normalize hemoglobin and ferritin levels. Clinically meaningful outcomes also include reducing the need for blood transfusions, symptom alleviation, enhanced exercise capacity, improved quality of life, and fewer hospitalizations. Monitoring typically occurs 4 to 8 weeks after completing the initial treatment course to track progress and adjust therapy as needed.

According to the input, factors to consider when deciding to discontinue treatment with ferric carboxymaltose include post-repletion assessments of Hb, ferritin, and TSAT levels. Treatment should be immediately discontinued in cases of hypersensitivity reactions

or intolerance during administration, and it is contraindicated in patients with iron overload or persistent hypophosphatemia, where re-evaluation of treatment is warranted. Ferric carboxymaltose is appropriate for treatment in settings equipped to manage anaphylaxis and hypersensitivity reactions. It can also be administered in emergency departments or surgical inpatient units when indicated. While specialists like hematologists and other physicians commonly prescribe ferric carboxymaltose, a specialist is not always required for diagnosis, treatment, and monitoring. Family medicine practitioners, as well as specialists in cardiology, gastroenterology, internal medicine, nephrology, and obstetrics/gynecology, among others, may also manage patients requiring IV iron therapy.

Drug Program Input

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

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of 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	
Relevant comparators may include ferric derisomaltose (Monoferric), iron sucrose (Venofer, generics) and sodium ferric gluconate complex (Ferrlecit) – although they don't have a specific HC indication for ID in patients with HF. Are these all considered relevant comparators? The comparator in the submitted trials was placebo or standard of care. Would a direct comparison against an off-label IV iron have been more appropriate or informative?	The clinical expert noted to CDEC that to their knowledge, iron sucrose and ferric derisomaltose are relevant comparators, but sodium ferric gluconate complex (Ferrlecit) is not used in Canada in this population. Notably, in the other indication (IDA in pediatric and adult patients in whom oral iron was inadequate, intolerable or contraindicated), the clinical expert consulted for that indication noted that sodium ferric gluconate complex is rarely used and is intended for a very uncommon, niche population of patients. As such, it was not considered a relevant comparator for this review. The clinical expert agreed that a comparison to another IV iron, especially second- or third-generation formulations, would have been more appropriate and more informative than a comparison to placebo. The clinical expert noted that it is known that oral iron is less effective, especially in this population due to physiological impacts of HF that worsen the potential for iron uptake for oral formulations, and moreover oral iron is not recommended in the HF treatment guidelines in Canada or internationally; in conclusion, the most reasonable comparator would be another IV iron formulation.
Considerations for initiation of therapy	
The product monograph indicates that patients must have a confirmed diagnosis of ID based on appropriate lab tests. The ferritin levels used in the inclusion criteria of the trials are consistent, but hemoglobin levels vary.	The clinical expert expressed that the definition of ID should be based on Canadian treatment guidelines, and noted that hemoglobin levels can be low or changed for reasons other than ID, and is too blunt an instrument to diagnose ID.

Implementation issues	Response
How should ID be defined? Are there specific lab parameter thresholds related to ID that should be considered as initiation criteria in patients with HF?	In the 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure states that the most widely accepted definition of ID in this population is a serum ferritin < 100 µg/L or ferritin between 100 and 299 µg/L and transferrin saturation < 20%. However, it also states that ID can be difficult to diagnose in patients with HF and diagnosis should ideally be done in a clinically stable state, and furthermore, new biomarkers (such as soluble transferrin receptor, hepcidin, and reticulocyte hemoglobin) might improve the sensitivity and specificity of ID diagnosis in the future, and their clinical utility has yet to be shown. Suggested commonly-available tests for the work-up of ID and IDA in the guidelines include also investigations for several other suspected etiologies, including GI-related blood loss (fecal occult blood, upper and lower endoscopy), thyroid-related disorders (thyroid stimulating hormone), nutritional deficiency (B12), thalassemia or sickle cell disease (hemoglobin electrophoresis), multiple myeloma, amyloidosis, and other protein disorders (serum and urine protein electrophoresis), and other/multiple (peripheral smear, reticulocyte count/index, lactate dehydrogenase, haptoglobin, bone marrow biopsy). CDEC recommended that ferric carboxymaltose be initiated in patients who have ferritin ≤ 300 µg/L with a TSAT < 15%
Oral iron is the first-line therapy for most patients with ID and/or IDA (and is inexpensive). Should patients with ID and HF be required to trial at least one oral iron therapy or be intolerant or have a contraindication to oral iron therapy (similar to patients with IDA)? If so, what would be considered an appropriate trial in this patient population? How would intolerance or contraindication be defined?	The clinical expert noted to CDEC that oral iron is not recommended in patients with HF and ID and has been demonstrated to be insufficiently effective in this patient population. The expert explained that there are complex physiological reasons that a patient with HF typically has poorer uptake of oral iron than the general population as a result of their HF. Therefore, a patient with diagnosed HF and ID should not be required to trial any oral iron preparation nor should they need to be intolerant or have a contraindication to any oral iron therapy before receiving an IV iron formulation. The best clinical practice in HF and ID for iron repletion has been well-defined as IV iron formulations, exclusively, in the Canadian and multiple international treatment guidelines.
The AFFIRM-AHF trial for patients with acute heart failure and ID did not meet its primary endpoint. Should patients with acute heart failure be considered for coverage, or should coverage be limited to patients with chronic heart failure?	The clinical expert noted to CDEC that between acute or chronic HF, it is the patients with chronic disease who will generally have the greatest need for ongoing inpatient treatment and – in the context of ID – the greatest need for iron repletion. Depending on the etiology, a patient with acute HF that resolves after treatment of the acute episode may not require ongoing treatment thereafter. However, the clinical expert explained that, in most cases, there is no reason to exclude patients with acute HF and ID from iron repletion, and treatment guidelines do not distinguish between AHF and CHF in their recommendations for management of concurrent ID. Patients with acute HF may progress to chronic HF and the distinction between these categories may be uncertain. Additionally, patients with ID or IDA may typically benefit in exercise capacity and HRQoL given appropriate iron supplementation, and in the setting of HF, the recommended manner of providing iron supplementation is by IV formulations.
Considerations for continuation or renewal of therapy	
The product monograph notes that re-assessment of hemoglobin should be performed no earlier than 4 weeks post final Ferinject administration to allow adequate time for erythropoiesis and iron utilization.	The clinical expert highlighted that hemoglobin is a blunt instrument that, alone, should not be used to diagnose or evaluate ID. The clinical expert stated that reduced or changed hemoglobin level may have a wide variety of etiologies that may or may not be related to depleted

Implementation issues	Response
How would therapeutic response to supplemental iron be assessed in patients with ID and CHF? Is Hemoglobin level alone sufficient?	iron stores and could co-occur with HF, with or without ID (e.g., chronic kidney disease, inflammation, hemodilution, rarer nutritional deficiencies [vitamin B12, folic acid, thiamine], GI blood loss, medication side-effects, etc.) Hemoglobin is a standard assessment in the work-up of anemia in general as well as in the context of HF and ID, and additionally, lower hemoglobin levels are associated with worse outcomes in HF; however, hemoglobin alone provides an insufficient assessment of ID. Management of ID with parenteral iron requires monitoring, among other things, hemoglobin and other iron parameters such as ferritin and TSAT. The clinical expert underscored that the Canadian treatment guidelines suggest ferritin and transferrin saturation are measured as a common work-up for diagnosis of ID, but that new biomarkers continue to emerge as potential contenders for more sensitive and specific ID diagnosis. The clinical expert also noted that many patients with HF and ID are expected to require iron supplementation for the duration of their lifetime. As such, there was no threshold of any laboratory parameter under which the drug should be discontinued due to lack of efficacy. The expert stated that treatment should be required for as long as dictated by guideline criteria for ID-related IV iron replacement therapy. CDEC recommended that for renewal after initial authorization and each subsequent annual renewal, the physician must provide proof that the criteria listed in the initiation criteria in Table 1 still applies.
Considerations for discontinuation of therapy	
Under what circumstances should Ferinject be discontinued in a patient with HF and ID?	The clinical expert noted to CDEC that so long as guideline criteria for iron replacement therapy maintain, and aside from intolerable AE or patient or clinician decision or preference, there are no specific reasons to require discontinuation of ferric carboxymaltose in a patient with HF and ID.
Considerations for prescribing of therapy	
Doses can range from 500mg to 2000mg, depending on hemoglobin level and body weight. The maximum recommended dose of ferric carboxymaltose is 1000mg of iron per week; thus patients requiring higher doses will require a second dose administered a minimum of 7 days from the first dose. How often do patients with ID and HF require doses of iron greater than 1000mg?	The clinical expert was uncertain and expected it is uncommon.
Currently, coverage for IV iron by public drug programs is not restricted by specialist type.	This is a comment from the drug programs to inform CDEC deliberations.
Care provision issues	
Ferinject is administered intravenously. Patients need to be monitored for hypersensitivity reactions during and for at least 30 minutes after administration.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
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	This is a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
special programs or provided through health authorities.	

AE = adverse event; AHF = acute heart failure; CHF = chronic heart failure; GI = gastrointestinal; HF = heart failure; ID = iron deficiency; IDA = iron deficiency anemia; IV = intravenous.

Clinical Evidence

Systematic Review

Description of Studies

The studies included were FAIR-HF (N = 459), CONFIRM-HF (N = 304), and HEART-FID (N = 3065) in patients with CHF, and AFFIRM-AHF (N = 1132) in patients with AHF, all 4 of which are placebo-controlled, double-blind, randomized phase 3 (FAIR-HF and HEART-FID) or phase 4 (CONFIRM-HF and AFFIRM-AHF) trials in adults with HF and ID. Of these, 2 studies (FAIR-HF and CONFIRM-HF) were focused primarily on clinical efficacy outcomes such as exercise capacity and NYHA class, while the remaining 2 (HEART-FID and AFFIRM-AHF) were focused primarily on composite outcomes related to hospitalizations and deaths. The studies ranged in duration from approximately 6 months (FAIR-HF) to 12 months (CONFIRM-HF, HEART-FID, and AFFIRM-AHF).

The 3 CHF studies each had a maximum allowed left ventricular ejection fraction (LVEF) at screening or index visit, although the precise threshold varied: ≤ 40% (NYHA II) or LVEF ≤ 45% (NYHA III)in FAIR-HF, ≤ 45% in CONFIRM-HF, ≤ 40% in HEART-FID (although historically reduced LVEF was also allowed given specific circumstances). In AFFIRM-AHF, the inclusion criteria required that patients had < 50% LVEF within 12 months prior to randomization. All 4 included studies required serum ferritin <100 ng/mL, or 100 to 299 or 300 ng/mL with TSAT < 20%. At baseline, mean patient ages were approximately 68 to 71 years across the treatment groups, and the proportion of female patients ranged from 33% to 55%. All 4 studies included adult patients with NYHA class II or III HF. Although HEART-FID also included NYHA Class IV and AFFIRM-AHF included NYHA Classes I and IV, the overwhelming majority of patients belonged to NYHA class II or III, with very few patients belonging to Class IV (<4% in AFFIRM-AHF and <1% in HEART-FID) or Class I (<3% in AFFIRM-AHF). White race was disproportionately over-represented in all studies; 86% in HEART-FID, 95% in AFFIRM-AHF, and 99% to 100% in FAIR-HF and CONFIRM-HF. Comorbidities were common, including hypertension, dyslipidemia, diabetes, atrial fibrillation, angina pectoris, and others.

Efficacy Results

NYHA Class

The NYHA functional class system is a subjective but widely used classification used to determine CHF severity based on symptoms, where NYHA Class I suggests little to no symptoms of HF and Class IV is defined by the inability to carry on any physical activity without discomfort and the presence of symptoms even at rest.

For the outcome of change in NYHA Class from baseline, there was a benefit associated with ferric carboxymaltose compared to placebo in FAIR-HF at week 24 (odds ratio [OR]: 2.400; 95% confidence interval [CI], 1.551 to 3.715; P < 0.001) where an OR of greater than 1 indicates a benefit of ferric carboxymaltose, and in CONFIRM-HF at week 24 (OR[redacted], P = 0 .004) and week 52 (OR: [redacted] P < 0.001), where an OR of less than 1 indicates a benefit of ferric carboxymaltose compared to placebo. In AFFIRM-AHF, although the point estimate suggests benefit associated with ferric carboxymaltose at week 52 based on an OR of greater than 1 (OR: [redacted]), there was insufficient evidence to confirm a difference between the treatment arms because the 95% CI crossed the null. HEART-FID did not report this outcome.

6MWT

The 6-Minute Walk Test (6MWT) is a common, validated test that measures the distance a patient can walk on a hard, flat surface over a 6 minute period under clinician supervision, where longer distances represent better exercise capacity. This outcome was assessed in FAIR-HF, CONFIRM-HF, and HEART-FID, but not AFFIRM-AHF.

In FAIR-HF, the mean change from baseline in 6MWT at 24 weeks was [redacted] (standard deviation [SD] [redacted]) in the ferric carboxymaltose group compared to [redacted] (SD [redacted]) in the placebo group, and the between-group difference was [redacted] (SD [redacted]) meters ([redacted]). Because no 95% CI was presented for the between-group results, additional data was requested from the sponsor, who provided a post-hoc analysis of absolute differences on request to inform the GRADE analysis; according to this additional data, which may not follow the same analysis as described in the study's statistical analysis plan, the between-group difference was [redacted] meters.

In the CONFIRM-HF primary analysis at week 24, the change from baseline in 6MWT was [redacted]) [redacted]) meters in the ferric carboxymaltose and placebo groups, respectively. The least squares mean between-group difference was [redacted] (standard error [SE] [redacted].

In HEART-FID, as a component of the composite primary outcome, the mean change from baseline to 6 months (i.e., 24 weeks) in 6MWT was 8 (SD 60) and 4 (59 m), respectively. Because no between-group differences were presented numerically, additional information was requested from the sponsor to support the GRADE analysis, which reported the following: the mean change from baseline to week 24 in 6MWT distance was [redacted] meters in the ferric carboxymaltose group and [redacted] meters in the placebo group, with a between-group difference in change from baseline of [redacted] meters.

In the CONFIRM-HF secondary analyses at week 52, the least squares mean between-group difference was [redacted] m (95% CI, [redacted]). Sensitivity analyses using the per protocol (PP) set did not include reporting of between-group differences, but the within-group changes from baseline were similar to that of the Full Analysis Set (FAS) analyses; the treatment benefit was also consistent across pre-planned and post-hoc subgroup analyses on demographic and disease-related features, and in a supportive analysis without primary imputation for deaths and hospitalizations.

In the HEART-FID secondary analyses at week 52, the mean change 5 meters (SD 71) in the ferric carboxymaltose group and 4 meters (SD 72) in the placebo group. Between-group values were not reported numerically, so additional information was requested from the sponsor, in which it was reported that the mean change from baseline to week 52 was [redacted] and [redacted] meters for the ferric carboxymaltose and placebo groups, respectively, with a between-arm difference in change from baseline of [redacted] meters.

KCCQ

The KCCQ was reported by FAIR-HF (24 weeks), CONFIRM-HF (24 and 52 weeks), and AFFIRM-AHF (24 and 52 weeks) as a secondary outcome in each case. It is a 23-item, self-administered questionnaire that quantifies physical limitation, symptoms (stability, frequency, and burden), self-efficacy, social function, and HRQoL. Scores are transformed to a range of 0 to 100, where higher scores reflect better health status. Although studies have been performed assessing its measurement properties and validity, the KCCQ is primarily a clinical trial tool and is not typically used in real-world clinical practice.

In FAIR-HF at week 24, the study treatment effect of ferric carboxymaltose was [redacted] greater in change from baseline of KCCQ overall summary score, compared to placebo ($P < 0.001$). Because there was no 95% CI provided with the point estimate for FAIR-HF, additional data was requested from the sponsor, which reported a between-group difference of [redacted] favouring ferric carboxymaltose.

In CONFIRM-HF at week 24, the least squared mean between-group difference was [redacted] points. In AFFIRM-AHF, the difference was [redacted].

In CONFIRM-HF at week 52, the between-group difference was [redacted] points, and in AFFIRM-AHF it was 1.44 (95% CI –1.45 to 4.33, P not reported)

Fatigue Score

Only CONFIRM-HF assessed the change from base line in fatigue score, ranked on a visual analogue scale from 0 to 10, where 0 implies no fatigue and 10 represents very severe fatigue. Some assessments of validity exist for this method of measuring fatigue, but there is no established MID. At week 24 the between-group difference (as least squares mean) in change in fatigue score was [redacted], and at week 52 it was [redacted].

Serum Ferritin

At baseline, mean serum ferritin values were below the threshold of 100 ng/mL that defines ID in the context of HF in all included studies.

At week 24, across all studies, the ferric carboxymaltose groups had mean serum ferritin levels of greater than 100 (although note that patients may still have "functional ID" if their TSAT is <20% and their serum ferritin is 100 to 300 ng/mL, as previously discussed), while the mean serum ferritin levels in the placebo groups were near or below 100 ng/mL.

In FAIR-HF at week 24, the between-group difference in absolute mean serum ferritin was [redacted] in the ferric carboxymaltose group and [redacted] ng/mL at in the placebo group ($p < 0.0001$).

In CONFIRM-HF, between-group values were not reported, but the mean serum ferritin at week 24 was [redacted] in the ferric carboxymaltose group, representing a mean change from baseline of [redacted], and in the placebo group the mean serum ferritin was [redacted] representing a change from baseline of [redacted]. Additional data was provided by the sponsor upon request, in which it was reported that the between group difference in change from baseline was [redacted].

Numerical values for serum ferritin were not reported in HEART-FID, although graphical representation can be found in the supplementary documents. Additional data was provided by the sponsor upon request, in which it was reported that the between group difference in change from baseline was [redacted] at week 24.

In AFFIRM-AHF, at week 24, the mean (SD) change from baseline was [redacted] in the ferric carboxymaltose group compared to [redacted] in the placebo group; no between-group differences were reported. Additional data was provided by the sponsor upon request, in which it was reported that the between group difference in change from baseline was [redacted] at week 24.

At week 52, the mean serum ferritin levels in the ferric carboxymaltose groups of CONFIRM-HF, HEART-FID, and AFFIRM-AHF were all in excess of 100 ng/mL but were lower than 300 ng/mL. FAIR-HF was a 24-week study so there are no 52-week values. In the placebo groups, the levels were close to or below 100 ng/mL.

In CONFIRM-HF at 52 weeks, between-group values were not reported, but the mean serum ferritin ng/mL (SD) at week 52 in the ferric carboxymaltose group was [redacted] representing a change from baseline of [redacted], and in the placebo group was [redacted] representing a change from baseline of [redacted]. Additional data was provided by the sponsor upon request, in which it was reported that the between group difference in change from baseline was [redacted] at week 52.

Values for serum ferritin were not reported in HEART-FID, although graphical representation can be found in the supplementary documents. Additional data was provided by the sponsor upon request, in which it was reported that the between group difference in change from baseline was [redacted] at week 52.

In AFFIRM-AHF, at week 52, the mean (SD) change from baseline was [redacted] in the ferric carboxymaltose group compared to [redacted] in the placebo group; no between-group differences were reported. Additional data was provided by the sponsor upon request, in which it was reported that the between group difference in change from baseline was [redacted].

CV Hospitalizations

De novo analyses of cardiovascular (CV) hospitalization rate were provided by the sponsor upon request to assist in the review. Through both 26 and 52 weeks, the between-group difference in event rate per 100 patient-years was lower in the ferric carboxymaltose groups than the placebo groups. Through 26 weeks, the between-group difference in event rate per 100 patient-years (95% CI) for ferric carboxymaltose versus placebo was [redacted] in FAIR-HF, [redacted] in CONFIRM-HF, [redacted] in HEART-FID, and [redacted] in AFFIRM-AHF. Through week 52, the between-group differences were [redacted] in CONFIRM-HF, [redacted] in HEART-FID, and [redacted] in AFFIRM-AHF.

HEART-FID and AFFIRM-AHF both had composite primary efficacy endpoints that included hospitalization-related outcomes; these will be discussed briefly here.

In the hierarchical composite primary endpoint of HEART-FID, death had occurred in 131 patients (8.6%) in the ferric carboxymaltose group and in 158 (10.3%) in the placebo group at 12 months, there were 297 and 332 total hospitalizations for heart failure by 12 months, respectively, and the mean change in the 6-minute walk distance from baseline to 6 months was 8 (SD 60) and 4 (SD 59) m, respectively (overall P = 0.02). The unmatched win ratio for the hierarchical composite outcome in the ferric carboxymaltose group as compared with the placebo group was 1.10 (99% CI, 0.99 to 1.23). Results of prespecified sensitivity analyses that included different imputation methods was reported to be consistent with those of the primary analysis. Because more than half the patients underwent randomization after March 2020, the censoring of data after the onset of the COVID-19 pandemic would have excluded the majority of follow-up data from the analyses.

In the primary efficacy endpoint of AFFIRM-AHF, which was a composite of recurrent HF hospitalizations and CV deaths up to 52 weeks after randomization, the annualized event RR for ferric carboxymaltose versus placebo was 0.79 (95% CI, 0.62 to 1.01), P = 0.059. In the pre-specified COVID-19 sensitivity analysis, the annualized event RR for ferric carboxymaltose versus placebo was 0.75 (95% CI, 0.59 to 0.96), P = 0.024.

CV Mortality

De novo analyses of CV mortality were provided by the sponsor upon request to assist in the review. Through both 26 and 52 weeks, minor and inconsistent differences were observed, with 95% CIs that always crossed null. Through 26 weeks, between-group the risk difference (95% CI) comparing ferric carboxymaltose to placebo was [redacted] in FAIR-HF, [redacted] in CONFIRM-HF, [redacted] in HEART-FID, and [redacted] in AFFIRM-AHF. Through 52 weeks, the values were [redacted] in CONFIRM-HF, [redacted] in HEART-FID, and [redacted].

Harms Results

Adverse Events

In FAIR-HF the proportion of patients who experienced at least 1 AE was [redacted] in the ferric carboxymaltose group and [redacted] in the placebo group, while in CONFIRM-HF the values were 79.6% and 75.7%, respectively. Overall AEs of any severity were not reported in HEART-FID. In AFFIRM-AHF, at least 1 AE was experienced by [redacted] patients in the ferric carboxymaltose group and [redacted] patients in the placebo group.

Common AEs that occurred in at least 5% of any one treatment group across FAIR-HF and CONFIRM-HF included cardiac failure, atrial fibrillation, angina pectoris, bronchitis, respiratory tract infection (viral), nasopharyngitis, influenza, increased blood pressure, hypertension, hypotension, headache, dizziness, and skin or subcutaneous tissue disorders. For the most part, the proportion of patients experiencing these events were relatively similar between treatment groups. Cardiac failure (chronic) appeared to be slightly less common in the ferric carboxymaltose group than the placebo group (FAIR-HF: [redacted] CONFIRM-HF: [redacted]). Common AEs that occurred in at least 5% of either treatment group in AFFIRM-AHF included cardiac failure, infections, gastrointestional (GI) disorders, nervous system disorders, metabolism and nutrition disorders, renal and urinary disorders, vascular disorders, injury, and musculoskeletal disorders.

Serious Adverse Events

In FAIR-HF, a total [redacted] in the ferric carboxymaltose group and [redacted] in the placebo group reported at least 1 serious adverse event (SAE). The most common SAE was cardiac disorders ([redacted] in the FCM and placebo groups, respectively).

In CONFIRM-HF, 43 patients (28.3%) in the ferric carboxymaltose group and 53 patients (34.9%) in the placebo group reported at least 1 SAE. The most common SAE was cardiac disorders ([redacted] in the FCM and placebo groups, respectively).

In HEART-FID, SAEs were reported in 581 patients (37.9%) in the ferric carboxymaltose group and 537 patients (35.0%) in the placebo group. The most common SAEs during the treatment period were pneumonia, reported in 57 patients (3.7%) in the ferric carboxymaltose group and 35 patients (2.3%) in the placebo group; acute kidney injury, reported in 46 patients (3.0%) in the ferric carboxymaltose group and 40 patients (2.6%) in the placebo group; and COVID-19, reported in 39 patients (2.5%) in the ferric carboxymaltose group and 37 patients (2.4%) in the placebo group. One event in the ferric carboxymaltose group was classified as hypophosphatemia. This event resolved and FCM treatment was continued.

In the AFFIRM-AHF, SAEs occurred in 250 (44.7%) of 559 patients in the ferric carboxymaltose group and 282 (51.2%) of 551 patients in the placebo group. The most common were cardiac disorders (in the FCM and placebo groups, respectively), followed by infections and infestations (in the FCM and placebo groups, respectively), followed by general disorders and administration site conditions (in the FCM and placebo groups, respectively). Other SAEs were less common.

Withdrawals due to AEs

In FAIR-HF, in the ferric carboxymaltose group and in the placebo group withdrew from the study treatment due to AEs; in CONFIRM-HF, this occurred among in the ferric carboxymaltose group and in the placebo group; in HEART-FID, and ; and in AFFIRM-AHF, , respectively.

Deaths

In FAIR-HF, five deaths occurred in the ferric carboxymaltose group ( ) and four in the placebo group ( ). During the study period, patients from the FCM group and from the placebo group died. In the ferric carboxymaltose group, three patients died due to sudden death, due to ischemic stroke, and due to severe anemia after terminating the study early. In the placebo group, patients died due to myocardial infarction, pulmonary edema, and sudden death.

In CONFIRM-HF, a total of in the ferric carboxymaltose group and in the placebo group died during the study period. The majority of deaths ( ) were related to cardiac disorders and cardiac-related TEAEs in other system organ classes (e.g., sudden cardiac death and cardiac death in the category of general disorders and administration site conditions). Two patients in the placebo group died of non-cardiac disorders (staphylococcal sepsis and acute renal failure).

In HEART-FID, death from any cause occurred in 361 patients (23.6%) in the ferric carboxymaltose group and 376 patients (24.5%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.78 to 1.05). The hazard ratio for death from any cause through month 12 was 0.82 (95% CI, 0.65 to 1.05). It is unknown how many deaths were due to AE.

In AFFIRM-AHF, patients in the ferric carboxymaltose group and in the placebo group had TEAEs resulting in death. The majority of deaths were related to cardiac disorders and cardiac-related TEAEs in other organ classifications (e.g., sudden cardiac death and cardiac death in the category of general disorders and administration site conditions).

Notable Harms

Hypophosphatemia is a notable harm associated with ferric carboxymaltose treatment that is not as highly associated with other IV iron formulations.

There were no reported cases of hypophosphatemia as TEAEs in both FAIR-HF and CONFIRM-HF studies.

In FAIR-HF, transient decreases in phosphate levels were observed in the ferric carboxymaltose group and this was reported to be most pronounced at week 4, but there were no clinical consequences, sequelae or interventions associated with this change. Differences between treatment arms were observed in the percentage of patients with values outside the normal range were observed for phosphate during follow-up (in the ferric carboxymaltose group versus in the placebo group placebo, P = 0.008).

In CONFIRM-HF, the minimum recorded serum phosphorus value was in two patients (one in the ferric carboxymaltose group and one in the placebo group), where hypophosphatemia is typically defined as < 2.5 mg/dL. Among all patients, experienced severe hypophosphatemia based on the CEC threshold of 0.3 to less than 0.6 mmol/L, although the investigators did not report these as TEAEs.

The overall incidence of hypophosphatemia was not reported in HEART-FID, but 1 SAE of hypophosphatemia reportedly occurred in 1 patient in the ferric carboxymaltose group and none in the placebo group. This hypophosphatemia event was considered by the investigator to be unrelated to ferric carboxymaltose; the event resolved and ferric carboxymaltose was continued.

In AFFIRM-AHF, there were cases of hypophosphatemia reported, of which was in the ferric carboxymaltose group and was in the placebo group.

Critical Appraisal

The overall risk of bias with regards to internal validity was low for the randomization process, allocation concealment, and maintenance of blinding.

Concerns for potentially important missing data were present for most outcomes assessed in at least one contributing study.

With regards to the outcomes assessed in this review, the primary efficacy analyses of FAIR-HF (i.e., NYHA class) and CONFIRM-HF (i.e., 6MWT) were adjusted for multiplicity, but other outcomes from these studies were not.

In supportive analyses of CONFIRM-HF using the PP set instead of the FAS, the sample size was substantially reduced from the FAS due to a high number of protocol violations, especially in the active treatment arm, which may result in a risk of bias due to deviations from the intended interventions.

The external validity and applicability of the results of this review are limited by the absence of any direct or indirect evidence comparing ferric carboxymaltose with other IV irons, which are its direct comparators in patients with HF and ID despite having no specific indication amongst the HF population in Canada at this time. No conclusions can be drawn from any of the submitted evidence on the relative efficacy or safety of ferric carboxymaltose with any other available IV iron formulation in patients with HF and ID. Additionally, there may be generalizability concerns regarding the demographics of the studies. The proportion of patients identified as white race was disproportionately high across the trials, particularly in FAIR-HF and CONFIRM-HF (98% to 100% across the treatment arms) but this was also generally true in the other two studies (85% and 95%). The trials were primarily conducted in countries other than Canada, and so demographic features as well as clinical practice related to both ID and HF individually and together may differ. HEART-FID included US sites, but the other 3 included studies were conducted primarily in Eastern Europe with some sites in Western Europe, Oceania, Asia, and/or South America, and so the clinical practices and patient characteristics may differ from those in Canada. Additionally, HEART-FID was the most recently conducted study and had the most inconsistent results, especially with regards to 6MWT, when compared to the other included studies; the reason for this inconsistency is not certain, but it may be related to changes in clinical practice and standard of care over time.

The proposed reimbursement request in HF is specific to patients of NYHA class II/III. However, this does not reflect the treatment guidelines, which do not specify any particular NYHA class in its recommendations for IV iron repletion therapies. AFFIRM-AHF enrolled patients with a broader range of NYHA classes (I to IV inclusive), and HEART-FID in patients with CHF also enrolled patients in NYHA class IV. However, the number of patients of NYHA class I and/or IV was proportionally very low in both studies.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, and input received from the clinician group and public drug programs. The following list of outcomes was finalized in consultation with expert committee members:

- HF disease severity as measured by NYHA score
- Exercise capacity as measured by change in 6MWT from baseline
- HRQoL as measured using change from baseline in KCCQ
- Fatigue Score
- Change from baseline in serum ferritin
- CV hospitalization rate
- CV mortality risk

Table 3: Summary of Findings for Ferric Carboxymaltose Versus Placebo for Patients with CHF and ID

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
HF Disease Severity				
NYHA Class Follow-up: 24 weeks	708 (2 RCTs)	**FAIR-HF (OR >1 favours FCM)** • FCM n = 294 • PBO n = 150 • OR (95% CI): 2.40 (1.55, 3.72) **CONFIRM-HF (OR <1 favours FCM)** • FCM n = 132 • PBO n = 132 • OR (95% CI): [redacted]	Moderate[a,b,c,d]	FCM likely results in an improvement in NYHA class at 24 weeks when compared with placebo, although it is uncertain whether the magnitude of difference is clinically important.
NYHA Class Follow-up: 52 weeks	248 (1 RCT)	**CONFIRM-HF (OR <1 favours FCM)** • FCM n = 127 • PBO n = 121 • OR (95% CI): [redacted]	Moderate[a,b,d]	FCM likely result in an improvement in NYHA class from at 52 weeks when compared with placebo, although it is uncertain whether the magnitude of difference is clinically important.
Exercise Capacity				
Change in 6MWT from Baseline, mean meters (95% CI) Longer distances represents better exercise capacity MID: 15 m Follow-up: 24 weeks	3243 (3 RCTs)	**FAIR-HF** • FCM n = 268: [redacted]m (NR) • PBO n = 134: [redacted]m (NR) • Difference: [redacted][e] **CONFIRM-HF** • FCM n = 130: [redacted] • PBO n = 131: [redacted] • LSM Difference: [redacted] **HEART-FID** • FCM n = 1285: [redacted] • PBO n = 1295: [redacted] • LSM Difference: [redacted]	Very low[d,f,g]	The evidence is very uncertain about the effect of FCM on change in 6MWT from baseline when compared with placebo due to large unexplained inconsistency between the study results and imprecision.
Change in 6MWT from Baseline, mean meters (95% CI) Longer distances represents better exercise capacity	2495 (2 RCTs)	**CONFIRM-HF** • FCM n = 125: [redacted] • PBO n = 121: [redacted] • LSM Difference: [redacted] **HEART-FID** • FCM n = 1140: [redacted][e] • PBO n = 1109: [redacted][e] • LSM Difference: [redacted]	Very low[d,f,g]	The evidence is very uncertain about the effect of FCM on change in 6MWT from baseline when compared with placebo due to large unexplained inconsistency between the study results and imprecision.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
MID: 15 m Follow-up: 52 weeks				
Patient-reported Outcomes				
Change in KCCQ Overall Summary Score from Baseline, mean score from 0 to 100 (95% CI) Higher score represents better HRQoL Follow-up: 24 weeks	690 (2 RCTs)	**FAIR-HF** • FCM n = 286: [redacted] • PBO n = 145: [redacted] • Difference: [redacted] **CONFIRM-HF** • FCM n = 125: [redacted] • PBO n = 124: [redacted] • LSM Difference: [redacted]	Low[a,b,d,f]	FCM may result in an improvement in KCCQ overall summary score compared with placebo, but it is uncertain whether the magnitude of difference is clinically meaningful.
Change in KCCQ Overall Summary Score from Baseline, mean score from 0 to 100 (95% CI) Higher score represents better HRQoL Follow-up: 52 weeks	220 (1 RCT)	**CONFIRM-HF** • FCM n = 114: [redacted] • PBO n = 106: [redacted] • LSM Difference: [redacted]	Moderate[a,b,d]	FCM likely results in an improvement in KCCQ overall summary score compared with placebo, but it is uncertain whether the magnitude of difference is clinically meaningful.
Change in Fatigue Score, mean score from 1 to 10 (95% CI) Higher score represents more severe fatigue Follow-up: 24 weeks	241 (1 RCT)	**CONFIRM-HF** • FCM n = 121: [redacted] PBO n = 120: [redacted] • LSM Difference: [redacted]	Moderate[a,b,d]	FCM likely results in a decrease (improvement) in fatigue score when compared with placebo, but it is uncertain whether the magnitude of difference is clinically meaningful.
Change in Fatigue Score, mean score from 0 to 10 (95% CI)	213 (1 RCT)	**CONFIRM-HF** • FCM n = 110: [redacted] • PBO n = 103: [redacted] • LSM Difference [redacted]	Moderate[a,b,d]	FCM likely results in a decrease (improvement) in fatigue score when compared with placebo, but it is uncertain whether the magnitude of difference is clinically meaningful.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Higher score represents more severe fatigue Follow-up: 52 weeks				
Serum Ferritin				
Change in Serum Ferritin from Baseline, mean µg/L (95% CI) Follow-up: 24 weeks	3183 (3 RCTs)	**FAIR-HF** • FCM n = 257: [redacted] • PBO n = 113: [redacted] • Difference: [redacted] [e] **CONFIRM-HF** • FCM n = 124: [redacted] • PBO n = 123: [redacted] • Difference: [redacted] [e] **HEART-FID** • FCM n = 1279: [redacted] PBO n = 1287: [redacted] • Difference: [redacted] [e]	Moderate[b,d]	FCM likely results in an increase (improvement) in serum ferritin when compared with placebo and there is uncertainty regarding the magnitude of effect.
Change in Serum Ferritin from Baseline, mean µg/L (95% CI) Follow-up: 52 weeks	2603 (2 RCTs)	**CONFIRM-HF** • FCM n = 114: [redacted] • PBO n = 106: [redacted] • Difference: [redacted] [e] **HEART-FID** • FCM n = 1142: [redacted] • PBO n = 1127: [redacted] • Difference: [redacted]) [e]	Moderate[b,d]	FCM likely results in an increase (improvement) in serum ferritin when compared with placebo and there is uncertainty regarding the magnitude of effect.
CV Hospitalization				
Hospitalization Due to Any CV Reason, event rate per 100 patient-years (95% CI) [i] Follow-up: 26 weeks	3825 (3 RCTs)	**FAIR-HF** • FCM n = 304: [redacted] [e] • PBO n = 155: [redacted] [e] • Difference: [redacted] [e] **CONFIRM-HF** • FCM n = 150: [redacted] [e] • PBO n = 151: [redacted] [e] • Difference: [redacted] [e] **HEART-FID** • FCM n = 1532 [redacted] [e]	Moderate[b,d]	FCM likely results in a decrease (improvement) in annualized hospitalization rate per 100 patient-years when compared with placebo, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• PBO n = 1533: [redacted][e] • Difference [redacted][e]		
Hospitalization Due to Any CV Reason, event rate per 100 patient-years (95% CI) [i] Follow-up: 52 weeks	3366 (2 RCTs)	**CONFIRM-HF** • FCM n = 150: [redacted][e] • PBO n = 151: [redacted][e] • Difference: [redacted][e] **HEART-FID** • FCM n = 1532: [redacted][e] • PBO n = 1533: [redacted][e] • Difference: [redacted][e]	Moderate[b,d]	FCM likely results in a decrease (improvement) in annualized hospitalization rate per 100 patient-years when compared with placebo, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.
CV Mortality				
Mortality Due to Any CV Reason, risk difference (95% CI) Follow-up: 26 weeks	3825 (3 RCTs)	**FAIR-HF** • FCM: [redacted] of 304 died [e] • PBO: [redacted] of 155 died [e] • Risk difference: [redacted][e,j] **CONFIRM-HF** • FCM: [redacted] of 150 died [e] • PBO: [redacted] of 151 died [e] • Risk difference: [redacted][e,j] **HEART- FID** • FCM: [redacted] of 1532 died [e] • PBO: [redacted] of 1533 died [e] • Risk difference: [redacted][e,j]	Low[b,g,k]	FCM may result in little-to-no difference in CV mortality when compared with placebo at 26 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.
Mortality Due to Any CV Reason, risk difference (95% CI) Follow-up: 52 weeks	3366 (2 RCTs)	**CONFIRM-HF** • FCM: [redacted] of 150 died [e] • PBO: [redacted] of 151 died [e] • Risk difference: [redacted][e,j] **HEART-FID** • FCM: [redacted] of 1532 died [e] • PBO: [redacted] of 1533 died [e] • Risk difference: [redacted][e,j]	Low[b,g,k]	FCM may result in little-to-no difference in CV mortality when compared with placebo at 52 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.

6MWT = 6-minute walk test; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; FCM = ferric carboxymaltose; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LSM = least squared mean; NYHA = New York Heart Association; OR = odds ratio; PBO = placebo; RCT = randomized controlled trial.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] This outcome is subjective, but there was no suspected risk of bias due to adequate maintenance of blinding.

[b] No known MID so the target of certainty appraisal was any effect.

[c] Only FAIR-HF adjusted for multiplicity for this outcome (NYHA). With that exception noted, no studies adjusted for multiplicity for this or any other outcome in this table.
[d] –1 level for risk of bias due to missing data.
[e] This value was provided by the sponsor upon request to assist in the interpretation of the evidence. Note that the analysis is post-hoc and not necessarily represented in the Statistical Analysis Plan of the relevant study.
[f] –2 level for very serious inconsistency due to differences in magnitude of effect between the studies, wherein the 95% CIs of some studies are minimally overlapping or not overlapping.
[g] –1 level for serious imprecision. CI crosses thresholds between one set of: harm, no difference, or benefit.
[h] Although the CI could be rated down twice, it was judged to be a narrow CI and not a sufficient cause for concern.
[i] The total number of events for all patients in the treatment group was divided by the total subject-years of follow-up in that treatment group multiplied by 100. Follow-up duration is equal to time on study. Time on study (weeks) = (Last Known Date - Randomization Date + 1)/7.
[j] Risk difference is FCM – Placebo with 95% Miettinen-Nurminen CI.
[k] –1 level for indirectness. Based on clinical expert opinion, the duration of assessment is likely insufficient to identify a difference between treatment groups for this outcome.
Source: Additional information request for absolute differences results data, Clinical Study Reports for FAIR-HF and CONFIRM-HF, and publication and supplementary appendix of HEART-FID

Table 4: Summary of Findings for Ferric Carboxymaltose Versus Placebo for Patients with AHF and ID

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
HF Disease Severity				
NYHA Class, adjusted for baseline value Follow-up: 52 weeks	912 (1 RCT)	**AFFIRM-AHF (OR > 1 favours FCM)** [redacted]	Moderate[a,b,c,d]	FCM likely results an improvement in NYHA class at 52 weeks when compared with PBO in adult patients with AHF and ID, although it is uncertain whether the magnitude of difference is clinically important.
Exercise Capacity				
6MWT	NA	NA	NA	There was no data available to inform this outcome in patients with AHF and ID.
Patient-reported Outcomes				
Change in KCCQ Overall Summary Score from Baseline, mean score from 0 to 100 [95% CI]	835 (1 RCT)	**AFFIRM-AHF** • FCM n = 422: [redacted] • PBO n = 413: [redacted] • Difference (95% CI): [redacted][e]	Moderate[a,b,c,d]	FCM likely results in an improvement in KCCQ overall summary score when compared with PBO in adult patients with AHF and ID, although it is uncertain

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Higher score represents better HRQoL Follow-up: 24 weeks				whether the magnitude of difference is clinically important.
Change in KCCQ Overall Summary Score from Baseline, mean score from 0 to 100 [95% CI] Higher score represents better HRQoL Follow-up: 52 weeks	738 (1 RCT)	**AFFIRM-AHF** • FCM n = 368: [redacted] • PBO n = 370: [redacted] • Difference (95% CI): [redacted][e]	Low[a,b,c,d,f]	FCM may result in an improvement in KCCQ overall summary score when compared with PBO in adult patients with AHF and ID, although it is uncertain whether the magnitude of difference is clinically important.
Fatigue	NA	NA	NA	There was no data available to inform this outcome in patients with AHF and ID.
Serum Ferritin				
Change in Serum Ferritin from Baseline, mean µg/L Follow-up: 24 weeks	838 (1 RCT)	**AFFIRM-AHF** • FCM n = 420: [redacted] • PBO n = 418: [redacted] • Difference (95% CI): [redacted]	Moderate[b,c,d]	FCM likely results an increase (improvement) in serum ferritin when compared with PBO.
Change in Serum Ferritin from Baseline, mean µg/L Follow-up: 52 weeks	685 (1 RCT)	**AFFIRM-AHF** • FCM n = 339: [redacted] • PBO n = 346: [redacted] • Difference (95% CI): [redacted]	Moderate[b,c,d]	FCM likely results in an increase (improvement) in serum ferritin when compared with PBO.
CV Hospitalization				
Hospitalization Rate Due to Any CV Reason, event rate per 100 patient-years [95% CI] Follow-up: 26 weeks	1108 (1 RCT)	**AFFIRM-AHF** • FCM n = 558: [redacted][e] • PBO n = 550: [redacted][e] • Difference (95% CI): [redacted][e,g]	Moderate[b,c,d]	FCM results in a decrease (improvement) in hospitalization rate due to any CV reason when compared with PBO, although it is uncertain whether the magnitude of

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
				difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.
Hospitalization Due to Any CV Reason, event rate per 100 patient-years [95% CI] Follow-up: 52 weeks	1108 (1 RCT)	**AFFIRM-AHF** • FCM n = 558: [redacted] [e] • PBO n = 550: [redacted] [e] • Difference (95% CI): [redacted] [e,f]	Moderate[b,c,d]	FCM results in a decrease (improvement) in hospitalization rate when compared with PBO in adult patients with AHF and ID, although it is uncertain whether the magnitude of difference is clinically meaningful. A longer follow-up duration may be more informative for this outcome.
CV Mortality				
Mortality Due to Any CV Reason, risk difference [95% CI] Follow-up: 26 weeks	1108 (1 RCT)	**AFFIRM-AHF** • FCM: [redacted] per 100 [e] • PBO: [redacted] per 100 [e] • Risk difference: [redacted] fewer per 100 ([redacted] more per 100) [e,h]	Low[b,c,f,i,j]	FCM may result in little-to-no difference in CV mortality when compared with placebo at 26 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.
Mortality Due to Any CV Reason Follow-up: 52 weeks	1108 (1 RCT)	**AFFIRM-AHF** • FCM: [redacted] per 100 [e] • PBO: [redacted] per 100 [e] • Risk difference: [redacted] fewer per 100 ([redacted] more per 100) [e,h]	Low[b,c,f,i,j]	FCM may result in little-to-no difference in CV mortality when compared with placebo at 52 weeks, but the duration of follow-up available may be insufficient to fully evaluate this outcome.

6MWT = 6-minute walk test; AHF = acute heart failure; CI = confidence interval; CV = cardiovascular; FCM = ferric carboxymaltose; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; OR = odds ratio; PBO = placebo; RCT = randomized controlled trial.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] –1 for serious risk of bias caused by a high proportion of potentially important missing data.

[b] This outcome was not adjusted for multiplicity.

[c] No known MID so the target of certainty appraisal was any effect.

[d] –1 level for risk of bias due to missing data.

[e] This value was provided by the sponsor upon request to assist in the interpretation of the evidence. If this value represents an analysis outcome, note that the analysis is post-hoc and not necessarily represented in the Statistical Analysis Plan of the relevant study.

[f] –1 level for serious imprecision. No known MID so target of certainty appraisal was any effect.

[g] The total number of events for all patients in the treatment group was divided by the total subject-years of follow-up in that treatment group multiplied by 100. Follow-up duration is equal to time on study. Time on study (weeks) = (Last Known Date - Randomization Date + 1)/7.

[h] Risk difference is FCM – Placebo with 95% Miettinen-Nurminen CI.

[i] –1 level for indirectness. Based on clinical expert opinion, the duration of assessment is likely insufficient to identify a difference between treatment groups for this outcome.

[j] Although the CI includes possibility of both benefit and arm, the CI is relatively narrow actually around the null, so it was subjectively judged that this was not imprecise enough to warrant rating down a 2nd time for imprecision.

Source: Additional information request for absolute differences results data, and clinical study report of AFFIRM-AHF

Long-Term Extension Studies

No long-term extension studies were submitted for this indication.

Indirect Comparisons

No indirect comparisons were submitted for this indication.

Studies Addressing Gaps in the Evidence From the Systematic Review

Summary and Critical Appraisal of Meta-Analysis by Ponikowski et al. (2024)

Objective

The objective of the meta-analysis was to evaluate the effects of ferric carboxymaltose treatment on clinical events, such as hospitalizations and mortality, in patients with HF and ID using patient-level data from randomized, placebo-controlled trials of ferric carboxymaltose that enrolled adults with HF and iron deficiency.

Methods

Inclusion Criteria

Ponikowski et al. performed a pooled analysis of patient-level data from trials that met the following criteria: (1) adult patients with HF and ID (defined as ferritin <100 ng/mL or ferritin 100 to 300 ng/mL and TSAT <20%), (2) used ferric carboxymaltose as an active treatment for ID; (3) double-blind, randomized, placebo-controlled trials; (4) had at least 52 weeks of follow-up; (5) prospectively recorded clinical outcomes: first and recurrent HF and CV hospitalizations, CV death, and all cause death.

Included Studies

The meta-analysis ultimately included CONFIRM-HF, AFFIRM-AHF, and HEART-FID. Searches were conducted to identify any additional studies, but none were added per the eligibility criteria. The authors were able to access individual patient data for the included studies.

Endpoints

The pre-specified co-primary efficacy endpoints were:

1. a composite of recurrent (total) CV hospitalizations and death for any CV reason (CV death)
2. a composite of recurrent (total) HF hospitalizations and CV death

All above outcomes were based on events adjudicated independently by blinded event committees. All 3 ferric carboxymaltose trials used consistent criteria for adjudication, which were pre-specified in each trial.

The key secondary efficacy endpoints were: (i) time to first CV hospitalization or CV death; (ii) time to first HF hospitalization or CV death; (iii) rate of total HF hospitalizations; (iv) time to first HF hospitalization; (v) time to CV death; (vi) time to all-cause death; (vii) total CV hospitalizations; (v) time to CV death; (vi) time to all-cause death; (vii) total CV hospitalizations; (viii) time to first CV hospitalization; and (ix) total all-cause hospitalizations.

All primary and key secondary endpoints were examined through 52 weeks of follow-up (primary endpoints: set with a time window up to 408 days).

Data Analysis

Efficacy analyses were conducted on the full analysis population defined as all randomly assigned patients who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment. The safety population comprised all patients who

were randomly assigned and received at least 1 dose of study medication, and was used to assess baseline characteristics and analyse the frequency of adverse events.

A negative binomial regression model was used to analyse event rates, including recurrent hospitalizations. The models were adjusted for baseline haemoglobin and region as fixed effects. Study was included as a random effect. The between-trial heterogeneity was explored by including a treatment by study interaction and a Cochrane Q test. Time-to-event outcomes used Cox proportional hazard analyses and the models were adjusted for haemoglobin at baseline and region. To explore between-trial heterogeneity, the study effect was included as a fixed effect.

Several pre-planned subgroup analyses and sensitivity analyses were conducted. As the purpose of the sponsor presenting this meta-analysis was in part to discuss the impact of TSAT on efficacy results, the TSAT subgroup will be discussed briefly in this subgroup, but other subgroups will not be.

A sensitivity analysis incorporating the IRONMAN trial (which did not include ferric carboxymaltose) was also conducted to evaluate IV irons versus placebo, which will not be discussed in depth here. An additional sensitivity analysis was also conducted using all available follow-up data (i.e., beyond 52 weeks).

Results

Efficacy

The results were in favour of ferric carboxymaltose without the 95% confidence interval overlapping null for the co-primary composite endpoint of CV death and total CV hospitalizations (rate ratio = 0.86, 95% CI; 0.75 to 0.98; P = 0.029). Similarly ferric carboxymaltose was associated with a 17% relative rate reduction in total CV hospitalizations (rate ratio = 0.83; 95% CI; 0.73 to 0.96; *P* = 0.009) and a 16% relative rate reduction in total HF hospitalizations (rate ratio = 0.84, 95% CI; 0.71 to 0.98; *P* = .025). For the outcome of total HF hospitalizations and CV death, the result was in favour of ferric carboxymaltose however the 95% confidence interval overlapped null (0.75 to 1.01). For the outcome of time to CV death, the 95% confidence interval also crossed null more indicating that there was no statistically significant difference between the treatment arms. Similarly, there was no statistically significant difference for time to all-cause death. Rate reductions in the primary composite endpoints were mainly driven by the treatment effect on HF hospitalizations and CV hospitalizations, with no apparent effect on CV or all-cause mortality.

In terms of subgroup results, there was a significant interaction effect identified between TSAT tertile and the composite of CV hospitalization and CV death (interaction P = 0.019) and between TSAT tertile and CV death (interaction P = 0.035), where patients in a lower TSAT tertile were more likely to see treatment benefit than those in a higher TSAT tertile. Although not statistically significant, a similar pattern was observed for the effect of TSAT on total HF hospitalizations and CV death (interaction P = 0.095). There were some other subgroups identified regarding “numerically” different treatment effects by subgroup (e.g., across haemoglobin tertiles and HF aetiology); other than these, the effects of ferric carboxymaltose therapy on both of the primary efficacy endpoints, CV death, and all-cause death were similar across other subgroups examined.

Safety

The incidences of investigator-reported serious treatment-emergent adverse events (TEAEs), serious TEAEs leading to death, and serious TEAEs leading to study discontinuation were similar across treatment groups through week 52. No deaths were judged to be the cause of serious treatment-related TEAEs. The rate of serious treatment-emergent infections were 9.9 per 100 patient-years and 9.6 per 100 patient-years in the ferric carboxymaltose and placebo groups, respectively. Treatment appeared to be safe and well tolerated.

Critical Appraisal

The meta-analysis appears to be conducted appropriately. All of the included trials were placebo-controlled, double-blind, randomized phase 3 or 4 trials in adults with HF and ID. CONFIRM-HF was focused on clinical efficacy outcomes such as exercise capacity and NYHA class, although the study did report survival and HF or CV related outcomes as well. AFFIRM-AHF and HEART-FID were focused primarily on composite outcomes related to hospitalizations and death. All 3 trials were at least 12 months in duration. The studies differed in minor ways with regards to inclusion criteria, such as whether NYHA Class I or IV was included; in

CONFIRM-HF, only Class II and III were included, while HEART-FID additionally included Class IV and AFFIRM-AHF did not specify any exclusions based on NYHA class. This was not expected to represent an important difference in patient populations, in part because prescription of IV iron is not dependent on NYHA class and in part because very few patients outside of Class II and III were included in any study overall. There were also minor differences with regards to the upper limit of LVEF and the range of included hemoglobin levels, but altogether these were considered very similar. The definitions of ID were the same across the studies.

A key difference in study design is that AFFIRM-AHF required patients to be hospitalized for acute HF during enrollment, while CONFIRM-HF and HEART-FID required a hospitalization within the prior year (or, in the case of HEART-FID, hospitalization within prior 12 months *or* elevated N-terminal-pro-brain natriuretic peptide within 90 days of randomization). These differences are important to consider when interpreting the results but were not expected to pose a concern with regards to conducting a meta-analysis such as that presented in Ponikowski et al. (2024), and all of the studies do represent the patient population in question. The inclusion of AFFIRM-AHF, which involves hospitalized patients with acute HF, introduces a significant between-trial difference in design and patient population. However, HEART-FID is a substantially larger trial, so any skewing of results due to the more at-risk population in AFFIRM-AHF may not be substantial. A sensitivity analysis excluding AFFIRM-AHF could have been useful to address this difference in patient population. Despite this minor concern, the treatment effect in AFFIRM-AHF was not consistently the highest in magnitude. In fact, CONFIRM-HF generally showed the largest treatment effect but also had the widest 95% confidence intervals across all co-primary composite outcomes and their components. Further exploration into this observation may be warranted, but it does not discredit the meta-analysis results. In the publication, between-trial heterogeneity in treatment effect was explored and models were adjusted for baseline hemoglobin and region, which was considered appropriate. The study authors state that there was no identified heterogeneity between the trials for any primary or key secondary outcomes, and that the treatment arms appeared to be balanced by demographics.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with heart failure and NYHA class II/III to improve exercise capacity.
Treatment	Ferric carboxymaltose
Dose regimen	The sponsor estimated an average cumulative iron dose (i.e. a treatment course) of 1,500 mg per patient (weight-based and dependent on Hb levels). A single ferric carboxymaltose administration should not exceed either 15 mg iron/kg of body weight or 1000 mg of iron. 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 cost	$800 per treatment course
Comparators	• 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	No direct or indirect evidence was provided by the sponsor for the indicated population comparing ferric carboxymaltose to iron sucrose and ferric derisomaltose. FERGIcor and REPAIR-IDA open-labelled randomized control trials comparing ferric carboxymaltose to iron sucrose in patients with IBD and CKD, a 2017 published meta-analysis

Component	Description
	(comparing ferric carboxymaltose to iron sucrose, ferric derisomaltose, and oral iron in patients with irritable bowel disease), and two indirect treatment comparison (Pollock and Muduma 2019; Han et al. 2023) in several other indications.
Costs considered	Drug acquisition costs, administration costs
Key limitations	• The sponsor assumed equivalent efficacy and safety between ferric carboxymaltose and comparators is uncertain. The CDA-AMC clinical review report found that there is a lack of direct or indirect evidence comparing ferric carboxymaltose to other IV iron formulations for the treatment of ID in patients with HF. No conclusions can be drawn regarding the relative efficacy and safety of ferric carboxymaltose for this indication. Ferric carboxymaltose is associated with a risk of hypophosphatemia, as detailed in the product monograph, with implications for monitoring and treatment costs. 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. • Clinical expert feedback obtained by CDA-AMC noted that iron sucrose is not among the recommended treatments in the clinical practice guidelines published by the European Society of Cardiology (only ferric derisomaltose and ferric carboxymaltose) for this patient population. Therefore, iron sucrose is unlikely to be a relevant comparator in this indication and the expected cost-saving estimated from the comparison with iron sucrose is uncertain. • Variability exists in clinical practice on the approach to calculate total iron dose per treatment course 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 iron sucrose or ferric derisomaltose is highly uncertain. A scenario analysis including costs associated with monitoring and treating patients with non-severe hypophosphatemia estimated that cost savings would be reduced. Reimbursement of ferric carboxymaltose may lead to additional costs to the health care system that may not have been fully considered within this analysis.

Hb = hemoglobulin; HF = heart failure; IDA = iron deficiency anemia; IBD = inflammatory bowel disease; CKD = chronic kidney disease; ID = iron deficiency; NYHA = New York Heart Association.

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 introduces uncertainty in the anticipated budget impact of ferric caboxymaltose. 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 $404,491 over three years is highly uncertain.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for ferric carboxymaltose for the treatment of iron deficiency (ID) in adult patients with heart failure and New York Heart Association (NYHA) class II/III to improve exercise capacity. In their request, the sponsor identified the following issues:

- The sponsor requested that CDEC consider additional context when interpreting the HEART-FID results.
- The sponsor was of the view that the there is evidence that indicate that ferric carboxymaltose would rediue hospitalization in patients with ID and heart failure (HF).
- The sponsor indicated that there is an unmet need in patients with HF.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- new information provided by the sponsor (Meta-Analysis by Ponikowski et al.) to address an important clear gap in the evidence identified by CDEC
- feedback from one clinical specialist with expertise in the diagnosing and treating patients with HF
- feedback on the draft recommendation from one clinician groups formed of 16 clinical specialists with diverse expertise and another input from one cardiologist
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process
- feedback on the draft recommendation from the sponsor

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

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.

Initial Meeting date: October 23, 2024

Regrets: Four expert committee members did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: February 27, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: None