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

REIMBURSEMENT REVIEW

Patient and Clinician Group Input

ferric carboxymaltose (TBC)

(CSL Vifor)

Indication: Ferinject (ferric carboxymaltose) is indicated: for the treatment of iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older when oral iron preparations are not tolerated or are ineffective 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. The diagnosis of iron deficiency must be based on laboratory tests.

May 27, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Patient Group Input

No patient group input was submitted.

Clinician Group Input

CADTH Project Number: SR0842-000 and SR0852-000

Generic Drug Name (Brand Name): Ferric carboxymaltose (Ferinject)

Indication: Treatment of:

- Iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older when oral iron preparations are not tolerated or are ineffective.
- Iron deficiency (ID) in adult patients with heart failure and New York Heart Association (NYHA) class II/III to improve exercise capacity.

About Your Clinician Group

Given ID and IDA affect many patient populations, we have assembled a group of independent clinicians from multiple specialties to provide feedback.

Table 1: List of participants

First name	Last name	Areas of expertise
Shelley	Zieroth	Cardiologist
Gordon	Moe	Cardiologist
Ally	Murji	Gynecology/Obstetrics
Ann Kinga	Malinowski	Gynecology/Obstetrics
Heather	Vandermeulen	Hematologist
Kevin	Pottie	Primary care
Andrea	Lavoie	Cardiology
Anil	Gupta	Cardiology
Eileen	O'Meara	Cardiologist
Brian	Bressler	Gastroenterology
Neeraj	Narula	Gastroenterology
Louise	Moist	Nephrologist
Gordon	Moe	Cardiologist

Information Gathering

Product monograph, published literature, and personal experience.

Current Treatments and Treatment Goals

Iron deficiency (ID) occurs on a continuum and, if left untreated, will eventually progress to iron deficiency anemia (IDA). ID can develop across a spectrum of conditions and states that cause increased losses and/or decreased absorption, including heart failure (HF), chronic kidney disease (CKD), inflammatory bowel disease (IBD), heavy menstrual bleeding (HMB), and pregnancy, among others. ID can also be precipitated or aggravated by iron-poor nutrition, as may be the case in an otherwise well pediatric patient.

In the Canadian context, ID and IDA are common, affecting approximately 7% and 2% of the population, respectively, with higher rates in females than males. Even in the absence of anemia, ID affects patients' physical and cognitive performance. For patients

suffering from comorbid medical conditions, ID and IDA introduce additional burdens, exacerbating symptoms, accelerating disease progression, and worsening prognosis.

The key goals in the treatment of ID and IDA are the correction of the hemoglobin (Hb) deficit and repletion of iron stores, as well as the maintenance of iron stores over time. Correction is achieved using supplementation (either oral or intravenous [IV] iron products), whereas maintenance is often dependent on identifying and managing the underlying cause of ID. Treatment reduces symptoms and improves function, improving health-related quality of life.

The typical recommendations for the treatment of ID and IDA are to start with oral iron replacement, and, if this is unsuccessful, move to IV iron therapy. Oral iron is relatively safe, effective, and inexpensive. However, correction of IDA with oral iron is slow: treatment with ferrous salts (100–200 mg/day of elemental iron) may take up to 3 months to normalize Hb and replenish stores. A variety of oral iron supplements are available in Canada, with inconsistent evidence that newer, more expensive formulations (ie, iron polysaccharide complex or heme iron polypeptide) have fewer adverse effects than ferrous salts. Gastrointestinal (GI) side effects, in particular, are common and can have a detrimental impact on patient adherence to treatment.[1] Oral iron may also be ineffective for patients with GI tract impairment, chronic inflammatory conditions, or concomitant medication(s) that decrease absorption.

The notable exception to the recommendation to start with oral iron is in patients with HF, where ID prevalence reaches 50% and has been found to be an independent predictor of worse functional capacity, increased hospitalization, and mortality. These findings have prompted recommendations, including by the Heart Failure Society of America (HFSA) that IV iron is the preferred treatment for patients with HF (foregoing oral iron as first-line treatment), and that treatment begins when ID is recognized—regardless of whether IDA is present.[2,3] This distinguishes HF from other conditions that typically suggest treatment only once the state of IDA is reached.

IV supplementation can also rapidly deliver iron to patients unable to absorb sufficient amounts from the GI tract, unable to tolerate the required dose, and/or who require faster repletion. In addition, the IV administration route can benefit patients with chronic losses exceeding the replacement rate possible with oral iron, and/or receiving erythropoietin-stimulating agent (ESA) treatment leading to increased iron demands. Last, IV iron can facilitate repletion in patients with poor adherence to oral products, as the total required iron amount can be delivered in one or two doses.

In addition to ferric carboxymaltose (FCM), there are currently four other IV iron products approved in Canada: Ferrlecit® (sodium ferric gluconate complex in sucrose; 12.5 mg/mL), Monoferric® (ferric derisomaltose; 100 mg/mL), Venofer® (iron sucrose; 20 mg/mL), and pms-Iron Sucrose® (iron sucrose injection; 20 mg/mL).

Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Most of the IV iron products previously available in Canada required administration over a long period of time and/or with a series of sessions to attain a cumulative dose of 1000 mg. Further, none were indicated for use in pediatric populations or for the treatment of patients with ID and HF.

FCM can safely deliver high doses (up to 1000 mg) of iron as a single injection or infusion over 15 minutes (and in less time for lower doses). As such, substantial gains in convenience and reductions in costs may be achieved for both patients and healthcare systems, with fewer individual administrations and reduced need for multiple, long treatment visits. A streamlined administration

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[1] Samantha Moe, Allan K. Grill and G. Michael Allan. Newer iron supplements for anemia. Canadian Family Physician August 2019, 65 (8) 556. https://www.cfp.ca/content/65/8/556

[2] Salah, H. M., Savarese, G., Rosano, G. M. C., Ambrosy, A. P., Mentz, R. J., and Fudim, M. (2023) Intravenous iron infusion in patients with heart failure: a systematic review and study-level meta-analysis. ESC Heart Failure, 10: 1473–1480. https://doi.org/10.1002/ehf2.14310.

[3] Ponikowski P, Mentz RJ, Hernandez AF, et al. Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis. Eur Heart J. 2023;44(48):5077-5091. doi:10.1093/eurheartj/ehad586

schedule may also improve adherence and, as a result, achievement of treatment goals. Further, high-dose IV iron delivery allows for rapid relief of symptoms due to faster correction of the deficiency.

Compared to older IV iron products, newer products, such as FCM, have better safety profiles. These formulations have complex carbohydrate cores that bind elemental iron more tightly aInnd release it more slowly.[4] They also use carbohydrate fragments with reduced immunogenic activity, which lowers the risk of severe hypersensitivity reactions.[5] Additionally, the pH of FCM is physiologic, as is the osmolarity/osmolality of the dispersion. Thus, FCM may have distinct advantages over the previously available IV iron compounds and may fill a clear unmet medical need for IV iron products with fast administration time.

Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

FCM offers an additional IV iron formulation for patients with ID and IDA when oral iron preparations are not tolerated or are ineffective. FCM may also be administered, without a trial of oral iron, in clinical situations where there is a need for rapid iron delivery.

FCM is likely to be used in place of IV iron products that require administration over a long time period and/or a series of sessions to attain a cumulative dose of 1000 mg (ie, sodium ferric gluconate complex in sucrose and iron sucrose). FCM may also be used in place of ferric derisomaltose, as both products offer the ability to deliver high doses (1000 mg) of iron over short periods of time (30 minutes for ferric derisomaltose and 15 minutes for FCM, respectively). The ability to deliver a high dose in a single session is particularly valuable when urgent correction of anemia and repletion of iron stores is required.

FCM will be used for the same clinical indications as the other IV iron products. In addition, while other products may be used off-label, FCM is the only IV iron indicated for the pediatric population in Canada. Finally, FCM is the first IV iron with a specific indication in patients with HF to address the ID that reduces exercise capacity in this chronically inflamed population.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Most adult and pediatric patients 1 year of age and older with IDA are well suited for treatment with FCM when oral iron preparations are not tolerated or are ineffective. These patients are expected to respond and to do so rapidly. While repletion of iron stores with oral products may require administration over several months, correction following FCM treatment occurs within days to weeks. Most patients will also appreciate that FCM treatment is administered over a shorter infusion time and in fewer visits compared to most other IV iron products; these product features will be even more important to patients with higher iron needs and/or who experience economic consequences from limited work tolerance due to unresolved IDA. For example, women of reproductive age from immigrant, refugee, and other migrant populations may face less barriers in caring for their (often large) families if IDA can be rapidly corrected.

Further, patients with HF and ID are well suited for treatment, as ID in these patients is known to be particularly resistant to oral iron therapy, necessitating the need for IV iron supplementation. Since ID is an independent predictor of reduced functional capacity, increased hospitalization, and increased mortality for HF patients, guidelines from the Canadian Cardiovascular Society, the HFSA, and the European Society of Cardiology (ESC) all recommend starting patients with IV iron in preference to oral formulations—regardless of whether anemia is present. The recently updated ESC guideline for the diagnosis and treatment of chronic and acute HF specifically recommends FCM as a treatment for symptomatic HF patients with ID. Similarly, recent guidelines from the American

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[4] Layla Van Doren, Michael Auerbach; IV iron formulations and use in adults. Hematology Am Soc Hematol Educ Program 2023; 2023 (1): 622–629. doi: https://doi.org/10.1182/hematology.2023000495

[5] Blumenstein, I., Shanbhag, S., Langguth, P., Kalra, P. A., Zoller, H., & Lim, W. (2021). Newer formulations of intravenous iron: a review of their chemistry and key safety aspects – hypersensitivity, hypophosphatemia, and cardiovascular safety. Expert Opinion on Drug Safety, 20(7), 757–769. https://doi.org/10.1080/14740338.2021.1912010

College of Cardiology (ACC) recommend that in patients with HF with reduced ejection fraction (HFrEF) and ID with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life.[6,7]

Limited clinical evidence also suggests that FCM is safe for use in pregnant patients. In obstetrics, IV iron infusions are often used to treat IDA, before and after delivery. However, prior to the introduction of FCM, a high dose IV iron formulation was not available for use during pregnancy in Canada (per the product monograph, ferric derisomaltose should not be used). As such, the addition of FCM as a treatment option for IDA in pregnancy—with all its advantages over low dose IV iron—is eagerly anticipated, especially by prescribers who have previously used the product in Europe, where it has been approved for almost two decades. It is also expected that the availability of FCM will lead to updated guidelines for the treatment of IDA in this population.

Patients suited for treatment with FCM can be identified using routine laboratory testing (ie, complete blood count, serum ferritin, ± transferrin saturation [TSAT]). For patients with HF, the simple and widely used New York Heart Association (NYHA) class subjectively estimates functional ability.

As ferritin levels can be elevated in patients with inflammation, ID may be underdiagnosed if ferritin alone is used for diagnosis. For these patients, TSAT is an important marker, with a value <20% indicative of low plasma iron availability to tissues in both absolute and functional ID.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

In both clinical practice and clinical trials, hematologic response and iron parameters (ferritin and TSAT), are used to determine whether a patient is responding to treatment. Ideally, patients would experience normalization of their Hb, such that they are no longer anemic. Further, ferritin would rise to levels above those diagnostic of ID. The expected magnitude of the response will vary depending on the patient, recognizing that complete correction may not be possible due to comorbidities and/or ongoing blood loss. In these patients—and all treated patients—it is also clinically meaningful for other outcomes to be achieved, for example, avoiding blood transfusion, improving symptoms, increasing exercise capacity, enhancing quality of life, or reducing hospitalizations.

Response to treatment should be regularly monitored during treatment. In clinical practice, this typically occurs 4–8 weeks after the completion of the initial treatment course. Laboratory assays may overestimate serum iron and transferrin-bound iron in the 24 hours following FCM administration.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Post-iron repletion assessments (Hb, ferritin, ± TSAT) are considered when deciding to discontinue treatment with FCM. Reassessment should be performed no earlier than 4 weeks after the final dose to allow adequate time for erythropoiesis and iron utilization.

Some patients are more likely to require additional treatment including those with lower initial Hb, impaired parenteral iron absorption (eg, IBD or post bariatric surgery), ongoing blood losses (eg, HMB or CKD requiring hemodialysis), and comorbid chronic inflammation (eg, CHF).

Treatment should be stopped immediately in patients with hypersensitivity reactions or signs of intolerance during administration. Treatment should not be administered to patients with iron overload. Treatment should be re-evaluated in patients with persistent hypophosphatemia.

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[6] Salah, H. M., Savarese, G., Rosano, G. M. C., Ambrosy, A. P., Mentz, R. J., and Fudim, M. (2023) Intravenous iron infusion in patients with heart failure: a systematic review and study-level meta-analysis. ESC Heart Failure, 10: 1473–1480. https://doi.org/10.1002/ehf2.14310.

[7] Ponikowski P, Mentz RJ, Hernandez AF, et al. Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis. Eur Heart J. 2023;44(48):5077-5091. doi:10.1093/eurheartj/ehad586

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Appropriate settings for treatment with FCM are those where personnel and therapies are available for the treatment of anaphylaxis and other hypersensitivity reactions. In practice, this will often be hospital day units or infusion clinics attended by outpatients. Where facilities exist, FCM may be administered in the community, at clinics and pharmacies that provide infusion services. If treatment is indicated, the emergency department or surgical inpatient unit are also appropriate settings for treatment.

A specialist is not required to diagnose, treat, and monitor patients who might receive FCM. In addition to family medicine and hematology, several specialties need to use IV iron in their practice, including cardiologists, gastroenterologists, internists, nephrologists, and obstetricians/gynecologists; midwives and nurse practitioners may also manage ID and IDA.[8] However, as hospital privileges are necessary to order IV iron within that setting, specialists will most commonly prescribe FCM.

Additional Information

Another consideration is that in Canada, there have been recent shortages of prescription drugs, with over 2,700 reports were received by Health Canada during the 2022–2023 period. Drug shortages can negatively affect patient treatment plans.[9] The availability of a second option for high dose IV iron in case of a shortage would provide a safeguard against harmful treatment interruptions.

[8]INESSS. Avril 2022. Traitement au fer intraveineux chez l'adulte Rapport en soutien au protocole médical national et au modèle d'ordonnance individuelle préimprimée.
https://www.inesss.qc.ca/fileadmin/doc/INESSS/Ordonnances_collectives/Fer_intraveineux/INESSS_Traitement_fer_IV_GN.pdf

[9] Huyghebaert T, Svrcek C, Perry TL. How to navigate drug shortages with patients in primary care. Beneficial opportunities may exist beyond initial frustrations. 2024;70(2):85-86. doi:10.46747/cfp.700285

Conflict of Interest Declarations – Clinician Group

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

International Market Access Consulting (IMAC) assisted in a supportive role: specifically collected physicians' conflict of interest declarations.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

International Market Access Consulting (IMAC) provided background information in a supportive role.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Shelley Zieroth

Position: Professor of Medicine

Date: 07-05-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
CSL/Vifor	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Louise Moist

Position: Nephrologist

Date: 01-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer		X		
Lilly		X		
BI		X		
Otsuka		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Kevin Pottie

Position: Family Physician Researcher> – Dalhousie University

Date: 01-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CSL Vifor	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Brian Bressler

Position: Staff Gastroenterologist

Date: 30-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Celltrion	X			
Sandoz	X			
Eli Lilly	X			
Organon		X		
BMS		X		
Gilead		X		
Viatris		X		
Takeda				X
Abbvie				X
Janssen				X
Pfizer				X
Alimentiv				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Gordon Moe

Position: Cardiologist, Director Heart Failure Program

Date: 06-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Ann Malinowski

Position: Maternal-Fetal Medicine Specialist

Date: 27-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CSF Vifor	X			

* Place an X in the appropriate dollar range cells for each company

Declaration for Clinician 7

Name: Dr. Neeraj Narula

Position: Director of IBD Clinic at Hamilton Health Sciences

Date: 28-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			X	
Janssen		X		
Takeda		X		
Eli Lilly	X			
Fresenius Kabi	X			
Pfizer		X		
Viatris	X			
Sandoz	X			
Iterative Health			X	
Innomar Strategies		X		

* Place an X in the appropriate dollar range cells for each company

Declaration for Clinician 8

Name: Dr. Mark Belletrutti

Position: Director of IBD Clinic at Hamilton Health Sciences

Date: 29-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche Canada		X		
Sanofi Canada		X		
Octapharma Canada	X			
Novo Nordisk Canada	X			
Bayer Canada	X			

* Place an X in the appropriate dollar range cells for each company

Declaration for Clinician 9

Name: Dr. Eileen O'Meara

Position: Cardiologist - Montreal Heart Institute

Date: 29-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
American Regent**	N/A	N/A	N/A	N/A

* Place an X in the appropriate dollar range cells for each company

**All fees related to the Heart-FID trial were paid to my institutions HF research group.