CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

IRON ISOMALTOSIDE 1000 (MONOFERRIC — PHARMACOSMOS A/S)
Indication: For the treatment of iron deficiency anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy. The diagnosis must be based on laboratory tests.

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that iron isomaltoside 1000 (Monoferric) be reimbursed for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance or unresponsiveness to oral iron therapy only if the following conditions are met:

Conditions for Reimbursement

Prescribing Condition

1. The drug must be administered in a setting where appropriate monitoring and management of hypersensitivity reactions can be provided.

Pricing Condition

1. Reduced price.

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Reasons for the Recommendation

1. Four Phase III, multi-centre, open-label, parallel group, active-control, non-inferiority, randomized controlled trials (RCTs) (PROPOSE (N=351), FERWON-Nephro (N=1538), PROVIDE (N=511) and FERWON-IDA (N=1512)) compared iron isomaltoside 1000 to iron sucrose in patients with IDA. All four trials showed iron isomaltoside 1000 to be non-inferior to iron sucrose in raising and/or maintaining hemoglobin (Hb) levels.
2. At the manufacturer-submitted price of $45.00 per 100 mg/mL solution for intravenous infusion, iron isomaltoside 1000 is more costly than the publicly available price of iron sucrose at $37.50 per 100 mg/mL solution. While differences in infusion time and frequency may lead to savings in total costs with iron isomaltoside 1000 compared with iron sucrose (e.g., supplies, chair time, nursing time), CDEC felt that in addition to the limitations identified by CADTH within the sponsor's pharmacoeconomic analysis (particularly the exclusion of adverse events from the analysis), only considering data from the PROVIDE trial increased the uncertainty regarding the cost-effectiveness of iron isomaltoside 1000. CDEC also noted that the negotiated price of iron sucrose may be lower than the publicly listed price, which introduces further uncertainty.

Implementation Considerations

- The patient should have failed or be intolerant to maximal course of oral iron therapy.

Discussion Points

- Although CDEC recognized the potential quality-of-life and convenience benefits for patients associated with iron isomaltoside 1000 compared with iron sucrose (e.g., faster iron repletion, shorter administration time, reduced number of infusions needed), they concluded that the submitted clinical evidence only demonstrated non-inferiority of iron isomaltoside 1000 compared to iron sucrose based on an increase in hemoglobin from baseline.
- Iron isomaltoside 1000 may be associated with less chair and nursing time and associated with cost savings if labour costs are variable. In some settings, such as when amount of nursing time cannot be reduced, cost savings may not be realized. Potential health system benefits, such as the potential for improved patient treatment flow and increased capacity to treat other patients requiring infusions were not included in the pharmacoeconomic analysis. CDEC also noted that there would be no expected savings in administration time for iron isomaltoside 1000 in patients with chronic kidney disease receiving hemodialysis who will be required to be present for the entire duration of the dialysis, or for hospital inpatients.
- CDEC noted that the submitted evidence for iron isomaltoside 1000 only compared it with iron sucrose: no evidence was submitted comparing iron isomaltoside 1000 with alternative intravenous (IV) iron supplementation products available for the

treatment of IDA in Canada. Therefore, the non-inferiority of iron isomaltoside 1000 to IV iron products other than iron sucrose cannot be established.

- CDEC noted that the sponsor did not incorporate adverse events into the pharmacoeconomic model despite clinical evidence indicating that the type of severe adverse events experienced within the trial differed between treatments (severe dyspnea and pruritic rash, moderate syncope for iron isomaltoside 1000 and severe anaphylactic reaction for iron sucrose). CDEC felt that these differences in severe adverse events may be associated with different resource use costs.
- CDEC discussed the unknown long-term cost-effectiveness of iron isomaltoside in the treatment of iron deficiency anemia. The committee noted that the sponsor's economic evaluation only assessed costs over a 5-week period in patient populations that often require iron infusion replenishment for several years. From Week 6 onward, all patients in the model were considered responders to the iron supplements but were not assigned further treatment costs (e.g., no retreatment). CDEC considered that the sponsor's modelling of the costs and effects of iron isomaltoside 1000 at Week 6 onwards may not be reflective of the expected costs and effects of iron supplements in clinical practice.
- CDEC heard clinical expert opinion of patients who might be considered tolerant to but unresponsive to oral iron due to their medical conditions impairing the ability of oral iron supplementation to appropriately correct IDA (e.g. patients experiencing extensive bleeding or with impaired absorption of oral iron). Such patients may be eligible for more aggressive approaches to correcting their IDA such as IV iron supplementation.
- There is a scarcity of data on the number and conditions of patients who require long term or chronic IV iron supplementation and a lack of data on how many patients with IDA require IV iron therapy because of intolerance to or unresponsiveness to oral iron supplementation.

Background

Monoferric has a Health Canada indication for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance or unresponsiveness to oral iron therapy. Iron isomaltoside 1000 is a dextran-free parenteral iron product. It is available as sterile aqueous colloidal preservative-free solution for injection. Iron isomaltoside 1000 may be administered as an IV bolus injection, an IV drip infusion or as an injection into a dialyzer:

- IV bolus injections of iron isomaltoside 1000 may be administered up to 500 mg up to once a week at a rate of up to 250 mg iron/minute.
- IV drip infusions may be administered as a single iron isomaltoside 1000 dose up to 20 mg iron/kg body weight or as weekly infusions until the cumulative iron dose is reached.
- Iron isomaltoside 1000 may be directly injected into the venous limb of a dialyzer following the same procedures as an IV bolus injection.

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by the Common Drug Review: a systematic review of phase III and IV randomized control trials of Monoferric and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered a published indirect treatment comparison, input from a clinical expert(s) with experience in treating patients iron-deficiency anemia, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups, Crohn's and Colitis Canada (CCC) and the Kidney Foundation of Canada (KFOC), provided input for this review. The CCC submission indicated that in a patient with inflammatory bowel disease (IBD), blood loss due to gastrointestinal bleeding and malabsorption of iron from nutritional sources can cause anemia. The KFOC submission reported that most people with moderate-to-severe chronic kidney disease (CKD) develop anemia. Patients described the most common symptoms of iron deficiency anemia to be weakness, fatigue, low energy, shortness of breath, and poor concentration and compromised quality of life. It was indicated that IBD patients are often prescribed oral iron supplements or in serious cases iron IV infusion.

Patients indicated that when choosing iron supplementation therapies, they faced trade-offs between slower response (oral tablets) and the convenience of taking the treatment at home compared to iron infusions in a clinical setting which requires an appointment

and potentially missed school or work. Two patients who had experience using iron isomaltoside 1000 (Monoferric) expressed that it worked well (effective), fast (noticed improvement in their symptoms within a few days), and easy (single treatment, instead of previous every 6 to 8 weeks infusion); and although one patient did not experience adverse effects on Monoferric, another patient reported some reactions (including burning sensation in body, red face and ears, and heart palpitations) when the infusion first started. Additionally, patients expressed concern over their ability to cover the cost of Monoferric in the absence of drug insurance or employment.

Clinical Trials

The systematic review included four phase III, multi-centre, open-label, parallel group, active-control, non-inferiority RCTs of patients with IDA. PROPOSE (N = 351) and PROVIDE (N = 511) were the pivotal studies identified by the manufacturer and FERWON-Nephro (N = 1538) and FERWON-IDA (N = 1512) were identified with the CDR systematic search strategy.

Eligible patients for PROPOSE, FERWON-Nephro, PROVIDE and FERWON-IDA were randomized 2:1 into iron isomaltoside 1000 and iron sucrose. In PROPOPSE, patients were required to have CKD Stage 5 (CKD-5D), receiving hemodialysis and renal-related anemia and FERWON-Nephro included patients with non-dialysis-dependent CKD (NDD-CKD) and IDA. In PROVIDE and FERWON-IDA, patients with IDA caused by various etiologies and who had a documented intolerance or unresponsiveness to oral iron therapy or a need for rapid iron repletion identified by the investigators were eligible for enrolment.

It is unknown the extent to which missing data may or may not have affected the findings primary analyses in FERWON-Nephro, PROVIDE and FERWON-IDA as the results from sensitivity analyses using data imputation was unavailable. In PROPOSE, non-inferiority of results was consistent across different imputation methods, except when missing values were imputed as failures, signaling a potential source of bias as more patients receiving iron isomaltoside 1000 had missing data (9.0%) compared with iron sucrose (3.4%). Nearly half of screened patients in PROVIDE and FERWON-IDA were excluded which raises concerns that the findings may not be generalizable to those patients not studied, particularly in the pivotal trial of PROVIDE. Finally, all trials incorporated multiple statistical test at various time points for superiority and for various outcomes without adjustment of p-values.

Outcomes

The primary outcome measure in PROPOSE was the proportion of patients who maintained a hemoglobin level between 95 – 125 g/L (both values included) at 6 weeks, while in PROVIDE the primary endpoint evaluated efficacy by comparing the proportion of patients who achieved an increase in hemoglobin of > 20 g/L from baseline to any time from week 1 to week 5. FERWON-Nephro and FERWON-IDA had the same co-primary endpoint which measured (1) the proportion of patients with serious or severe hypersensitivity reactions and (2) the change in hemoglobin from baseline to 8 weeks.

Efficacy

The pivotal trials PROVIDE and PROPOSE showed iron isomaltoside 1000 to be non-inferior to iron sucrose for their respective primary endpoints of raising or maintaining hemoglobin levels and raising hemoglobin levels. In PROVIDE, more iron isomaltoside 1000 patients (full analysis set, FAS: 68.5%; per-protocol, PP: 70.1%) compared with iron sucrose (FAS: 51.5%; PP: 53.8%) achieved larger hemoglobin response (i.e. $\geq$ 20 g/L) from baseline to any time within 1 – 5 weeks and the risk difference in the PP dataset of 15.9% (95% CI 6.3, 25.4) showed iron isomaltoside 1000 to be non-inferior to iron sucrose as the lower end of 95% CI was > -12.5% points. The results in the FAS dataset were consistent with the PP dataset. In PROPOSE, the proportions of patients who were able to maintain hemoglobin between 95 – 125 g/L (both values included) in iron isomaltoside 1000 (83.9%) and iron sucrose groups (82.2%) were similar at six weeks and the adjusted risk difference in the PP data set of 2.2% points (95% CI -6.4, 10.9) concluded the treatments were non-inferior as the lower limit of 95% CI was higher than -10% non-inferiority margin. The finding of non-inferiority was consistent across FAS and PP datasets, as well as various data imputation methods with the exception of the FAS unadjusted analysis with missing values imputed as failures, signaling a potential source of bias.

The primary analysis of PROPOSE and PROVIDE tested for superiority, however only PROVIDE found iron isomaltoside 1000 to be superior than iron sucrose in raising hemoglobin levels as a statistically significantly greater proportion of iron isomaltoside 1000 patients achieved hemoglobin $\geq$ 20 g/L from baseline to anytime within 1 – 5 weeks compared with iron sucrose (FAS: $P < 0.0001$; PP: $P = 0.0002$). The superiority finding in PROVIDE was most likely related to maximum cumulative iron dose permitted during the

trial. PROVIDE patients were permitted to receive up to 2000 mg cumulative iron (the highest cumulative dose administered across the included trials), and iron isomaltoside 1000 patients compared with iron sucrose received a greater mean cumulative iron dose (1640.20 mg vs. 1127.9 mg, respectively). The primary efficacy endpoints were the same for FERWON-Nephro and FERWON-IDA trials. Both trials found iron isomaltoside 1000 to be non-inferior to iron sucrose on the ability to raise hemoglobin levels as measured by the mean change in hemoglobin levels from baseline to week 8. FERWON-IDA tested for superiority, however, iron isomaltoside 1000 was not found to be statistically superior at raising hemoglobin levels by 8 weeks as the 95% CI contained zero.

Of the secondary endpoints in PROPOSE, iron isomaltoside 1000 was statistically significantly better at raising *s*-ferritin levels, an indication of how well iron stores are replenished, from baseline to weeks 2 (treatment difference estimate 123.3600 µg/L (95% CI 96.449, 150.271; P < 0.0001)) which was attributed to the single dose iron isomaltoside 1000 arm. This showed that iron isomaltoside 1000 was better at replenishing iron stores earlier than iron sucrose. A secondary endpoint in the pivotal trial PROVIDE showed iron isomaltoside 1000 was statistically better at achieving a faster hemoglobin response compared with iron sucrose. The secondary analyses in FERWON-Nephro and FERWON-IDA, further supported findings that iron isomaltoside 1000 was better at achieving an earlier and greater hemoglobin response.

The health related QoL outcomes of energy, fatigue and overall quality of life were identified as important to patients and found not to be different for either treatment group across the included trials, with the exception of FERWON-IDA at week 1. In FERWON-IDA, the mean change in FACIT-FS from baseline to week 1 was statistically significant between iron isomaltoside 1000 and iron sucrose, indicating iron isomaltoside 1000 patients experienced a faster improvement in fatigue symptoms compared with iron sucrose. This difference in FACIT-FS was not seen at week 2 or 8 in FERWON-IDA. The clinical expert suggested a possible reason for the non-significant differences in QoL and fatigue and restless leg syndrome (RLS) was due to the fact that the cumulative doses received by iron isomaltoside 1000 and iron sucrose patients was comparable between treatment groups, with the exception of PROVIDE.

Harms (Safety)

The overall incidence of patients reporting at least one treatment emergent adverse event (TEAE) was similar in PROPOSE and PROVIDE and both trials showed the proportion reporting a TEAE to be slightly greater for iron isomaltoside 1000 patients compared with iron sucrose. In contrast, FERWON-IDA reported a lower and well-balanced incidence of TEAEs both treatment groups. The frequency of patients reporting at least one serious adverse event (SAE) was also higher in PROPOSE and PROVIDE compared with FERWON-IDA. The proportion of iron isomaltoside 1000 and iron sucrose patients reporting > 1 SAEs was similarly balanced between treatment groups for PROVIDE and FERWON-IDA. However, the proportion of patients reporting > 1 SAE in PROPOSE was higher for iron isomaltoside 1000 patients compared with iron sucrose patients in PROPOSE. The incidence of patients withdrawing from a trial due to an adverse event (AE) was also higher in PROPOSE and PROVIDE trials than in the FERWON-IDA trial. The type of AE experienced differed between treatments (severe dyspnea and pruritic rash, moderate syncope for iron isomaltoside 1000 versus severe anaphylactic reaction for iron sucrose). Patients in the iron isomaltoside 1000 group also reported more skin and subcutaneous tissue disorders as well as hypophosphatemia, while iron sucrose was associated with more nervous system and gastrointestinal disorders. The proportion of patients withdrawing from the study due to an AE was similarly balanced for iron isomaltoside 1000 and iron sucrose patients in PROVIDE and FERWON-IDA. The incidence of serious or severe hypersensitivity reactions were consistently low across the included trials.

Indirect Treatment Comparisons

The manufacturer did not include indirect comparison evidence in their submission. A supplemental literature search was conducted by CADTH for potential relevant indirect comparisons evidence and a potentially relevant systematic review and NMA was identified. The objective of the NMA by Aksan et. Al (2017) was to compare the efficacy and tolerability of different intravenous iron formulations and oral iron agents used to treat IDA in patients with inflammatory bowel disease. However, the NMA did not include any of the four studies (two pivotal and two non-pivotal studies) selected for this CADTH review, and the primary outcome was the therapy response (defined as Hb normalization or increase ≥20 g/L) which was not aligned with the key outcomes listed in the protocol for this CADTH review. In terms of results, the NMA reported that there was no statistically significant difference between iron isomaltoside 1000 and iron sucrose in terms of response rate in the treatment of IDA in patients with inflammatory bowel disease.

Cost and Cost-Effectiveness

Iron isomaltoside 1000 is available as 100 mg/mL of elemental iron, in 1 mL, 5 mL and 10 mL vial sizes, at submitted prices of $45, $225, and $450, respectively, or $45 per mL. The recommended total dose of iron isomaltoside 1000 may be calculated using the Ganzoni formula or a simplified table available within the product monograph, and is typically between 1000 mg and 2000 mg, leading to a drug cost of $450 to $900 per course of therapy.

The manufacturer submitted a cost-utility analysis comparing iron isomaltoside 1000 to iron sucrose for adults with IDA who have intolerance or unresponsiveness to oral iron therapy, from the perspective of a Canadian publicly-funded healthcare system over a six-month time horizon. Patients entered the model in the IDA health state, and at the end of the first week, transitioned into either a responder or a non-responder health state. Patients could become responders at any point during the first five weeks. Treatment efficacy, in terms of the proportion of patients who had responded to treatment (percentage of patients with a Hb increase of ≥ 20 g/L) in the first five weeks of the model, was based on the PROVIDE trial. Patients in the responder health state were assumed to have the average Canadian utility value, while non-responders were assigned a disutility reflective of patients with anemia in the US. From Week 6 onward, all patients in the model were assigned the utility value of responders. Cost inputs included the acquisition cost of iron therapy based on the mean received dose for each comparator in the PROVIDE trial. The number of infusions required was calculated by dividing the total mean dose by the maximum dose per infusion (i.e., 1,000 mg and 200 mg for iron isomaltoside 1000 and iron sucrose, respectively). Additional costs included those associated with drug administration.

CDR identified a number of limitations in the model submitted by the manufacturer:

- The health states, based on response as opposed to the absolute Hb level, were of uncertain relevance in terms of their relationship to utility values
- The number of infusions required for iron sucrose was likely overestimated compared to clinical practice, along with the number of monitoring tests required
- While the analysis was probabilistic, the majority of inputs relied on assumed variances rather than being informed by data
- The impact of adverse events associated with iron isomaltoside 1000 and iron sucrose administration was not considered

CADTH attempted to address some of the identified limitations by incorporating: a 300 mg dose of iron sucrose being administered per infusion; an equal number of laboratory tests for each comparator; and, the introduction of data-informed variance for nursing wages. In the CADTH base case, iron isomaltoside 1000 was dominant, costing $148.42 less than iron sucrose, due to administration cost savings, and was associated with 0.0026 more QALYs. However, the very small quality of life difference found between iron isomaltoside 1000 and iron sucrose remains uncertain along with the long-term cost-effectiveness of iron isomaltoside 1000.

When considering drug costs alone, iron isomaltoside 1000 was more expensive than iron sucrose. The cost savings associated with the use of iron isomaltoside 1000 were primarily due to administration cost savings which may benefit some budget holders (i.e., hospital budgets), while other payers may observe increased costs (i.e., public drug plans).

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 19, 2019 Meeting

Regrets

One member did not attend.

Conflicts of Interest

None

February 19, 2020 Meeting

Regrets

None

Conflicts of Interest

None

March 18, 2020 Meeting

Regrets

None

Conflicts of Interest

None