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CADTH Reimbursement Recommendation

Deferiprone (Ferriprox)

Indication: Treatment of patients with transfusional iron overload due to sickle cell disease or other anemias

Sponsor: Chiesi Canada Corp.

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Ferriprox?

CADTH recommends that Ferriprox should be reimbursed by public drug plans for the treatment of patients with transfusional iron overload due to sickle cell disease (SCD) or other anemias if certain conditions are met.

Which Patients Are Eligible for Coverage?

Ferriprox should be covered based on the criteria used by each of the public drug programs for deferasirox (DFX), the other orally administered treatment for transfusional iron overload for patients with SCD and other anemias.

What Are the Conditions for Reimbursement?

Ferriprox should only be prescribed by clinicians who have expertise managing SCD and if the cost of Ferriprox is not more than the lowest cost iron chelation therapy used to treat transfusional iron overload for SCD or other anemias.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial and an indirect comparison suggested that Ferriprox was similarly effective compared to deferoxamine (DFO) and DFX for reducing the concentration of iron in the liver of patients with transfusional iron overload.
- Ferriprox could help address some of these unmet needs by providing an alternative orally administered treatment option that can be used by patients with renal impairment.
- Based on CADTH's assessment of the health economic evidence, Ferriprox does not represent good value to the health care system at the public list price. There is insufficient evidence to justify a greater cost for Ferriprox compared with DFO and DFX.
- Based on public list prices, Ferriprox is estimated to cost the public drug plans approximately $9 million over the next 3 years.

Additional Information

What Is Transfusional Iron Overload?

Patients with SCD and other anemias who undergo chronic blood transfusions to manage their condition may experience an accumulation of excess iron overtime. This excess iron can lead to organ failure and/or death if patients do not receive treatment.

Unmet Needs in Transfusional Iron Overload

There is an unmet need for patients who: cannot receive DFX due to kidney function problems, experience intolerable side effects with DFX or DFO, or have problems adhering to the IV or subcutaneous treatment regimen with DFO.

How Much Does Ferriprox Cost?

Treatment with Ferriprox is expected to cost between $6,113 and $8,151 per month.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that deferiprone be reimbursed the treatment of patients with transfusional iron overload due to SCD or other anemias, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One 12-month, open-label, randomized, pivotal trial (FIRST; N = 230) demonstrated that orally administered deferiprone was noninferior to subcutaneously (SC) administered deferoxamine (DFO) for change from baseline in liver iron concentration (LIC) and serum ferritin (SF) in patients with SCD and other anemias who require iron chelation therapy for transfusional iron overload. The indirect comparison of deferiprone with both DFO and deferasirox (DFX) submitted by the sponsor showed similar efficacy between the iron chelators with respect to LIC and SF, however, the network meta-analysis (NMA) had limitations, including differences in the study populations and wide credible intervals for the relative estimates of effect. Considering the results of the noninferiority trial comparing deferiprone and DFO and the clinical opinion of the expert consulted by CADTH, CDEC concluded that, despite limitations with the NMA, the efficacy of deferiprone is similar to DFX and DFO for reducing LIC and SF at 12 months.

Patient groups indicated that they are seeking new treatments for transfusional iron overload that can improve cardiac, liver, and endocrine function; reduce the risk of premature death; improve patient adherence; and provide patients and prescribers with additional therapeutic options. Patients and clinicians also identified an unmet medical need for those with transfusional iron overload who are unable to receive DFX due to renal impairment; unable to tolerate DFX or DFO resulting in discontinuation or dose reduction to a level that is subtherapeutic; and those who have poor adherence to IV or SC administration with DFO. CDEC concluded that deferiprone could help address some of these unmet needs by providing an alternative orally administered treatment option that is not contraindicated in patients with renal impairment.

At the sponsor submitted price for deferiprone and publicly listed prices for DFX and DFO, deferiprone was more costly than both DFO and DFX. As deferiprone is considered to be similarly effective compared with DFO and DFX, the total drug cost of deferiprone should not exceed the total drug cost of DFO and DFX.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of deferiprone should be based on the criteria used by each of the public drug programs for the reimbursement of DFX.	Evidence from an indirect comparison demonstrated that the efficacy of deferiprone was similar to DFX, the other orally administered drug used for iron chelation therapy in patients with transfusional iron overload.	—

Reimbursement condition	Reason	Implementation guidance
Renewal		
2. Eligibility for renewal of reimbursement of deferiprone should be based on the criteria used by each of the public drug programs for the reimbursement of DFX.	There is no evidence that deferiprone should be held to a different standard than DFX when considering renewal.	—
Discontinuation		
3. Discontinuation of reimbursement of deferiprone should be based on the criteria used by each of the public drug programs for the reimbursement of DFX.	There is no evidence that deferiprone should be held to a different standard than DFX when considering discontinuation.	—
Prescribing		
4. Patients should be under the care of clinicians who have expertise in managing SCD or other anemias that are treated with red blood cell transfusion.	Treatment with deferiprone may be associated with rare but serious adverse events (e.g., severe neutropenia) and patients at risk of neutropenia should be carefully monitored.	Only physicians registered with the sponsor's-controlled distribution program are permitted to prescribe deferiprone.
Pricing		
5. The cost of deferiprone should be negotiated so that it does not exceed the drug program cost for the lowest cost iron chelation therapy used to treat transfusional iron overload associated with the treatment of SCD or other anemias.	Direct and indirect evidence demonstrated that the efficacy of deferiprone was similar to DFO and DFX. There was insufficient clinical evidence to evaluate the comparative safety of deferiprone, DFO, and DFX. As such, there is insufficient evidence to justify a cost premium for deferiprone over the least costly option reimbursed for transfusional iron overload associated with the treatment of SCD or other anemias.	—

AE = adverse event; DFO = deferoxamine; DFX = deferasirox; SCD = sickle cell disease.

Discussion Points

- CDEC noted that the FIRST trial excluded patients who were receiving treatment with hydroxyurea. The clinical expert noted that hydroxyurea is commonly used in Canadian clinical practice for the management of SCD patients. It was noted that patients receiving concomitant treatment with hydroxyurea and deferiprone would be carefully managed for the potential risk of neutropenia.
- Patient groups expressed a need for additional therapeutic options that can improve adherence to the treatment regimens for transfusional iron overload. Stakeholders noted that IV and SC administered DFO is typically the more challenging regimen for patients and that deferiprone would be valued as an additional orally administered treatment

option. CDEC noted that the dosage regimen recommended in the product monograph for deferiprone requires 3 times daily administration which can be a burden for patients, particularly in comparison with DFX where administration of both film-coated and dispersible tablets is once daily.

- CDEC also reviewed the Calvaruso et al. (2019) study and noted that the use of SF as the only efficacy end point was a major limitation, as this end point is not typically used in isolation to evaluate response to iron chelation in Canada. In addition, there were serious limitations with this study, including concerns about generalizability of the study population to the Canadian setting, the small sample size, and considerable loss to follow-up.
- CDEC noted that deferiprone may help address an unmet need for patients who are unable to receive DFX due to renal impairment.

Background

Deferiprone is an iron chelator that is approved for use in the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; and the treatment of patients with transfusional iron overload due to SCD or other anemias. The indication under consideration for this review is the treatment of patients with transfusional iron overload due to SCD or other anemias. SCD is an inherited blood disorder, affecting an estimated 5,000 Canadian patients. Patients with SCD usually have chronic anemia and may require blood transfusions. The approved indication for deferiprone does not identify what conditions are classified as 'other anemias' where patients require treatment for transfusional iron overload (i.e., those conditions other than SCD or thalassemia). These anemias are rare conditions and those studied in the pivotal trial for deferiprone included: congenital dyserythropoietic anemia, pyruvate kinase deficiency, hereditary spherocytosis, hemoglobin s-beta thalassemia, and dyserythropoietic anemia, autoimmune hemolytic anemia, other rare hemoglobinopathies, and chronic nonspherocytic hemolytic anemia.

Deferiprone is available as 1,000 mg oral tablets and a 100 mg/mL oral solution. The recommended dose is 25 mg/kg/day to 33 mg/kg/day based on body weight, taken orally, 3 times a day, for a total daily dose of 75 mg/kg/ to 100 mg/kg.

Sources of Information Used by the Committee

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

- A systematic review that included 2 open-label RCTs: FIRST (N = 213) and Calvaruso et al., 2014 (N = 60). The evidence systematic review was supplemented with 1 long-term extension phase study (FIRST-EXT; N = 134) and 1 indirect comparison submitted by the sponsor.
- Patient perspectives gathered by 2 patient groups, the Sickle Cell Awareness Group of Ontario (SCAGO) and the Thalassemia Foundation of Canada.
- Input from public drug programs that participate in the CADTH review process.

- A clinical specialist with expertise diagnosing and treating patients with transfusional iron overload due to SCD or other anemias.
- Input from 1 clinician group, the Canadian Hemoglobinopathy Association.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, SCAGO and the Thalassemia Foundation of Canada submitted patient input for this review. The Thalassemia Foundation of Canada reiterates their input submitted to CADTH in October 2015 for the initial review of deferiprone. The input gathered information from various sources including a search of the medical literature, a collection of focus group reports, clinical practice guidelines, and other organizations representing the interests of patients with SCD.

The Thalassemia Foundation of Canada stated, based on published literature, that it believes the symptoms of excess iron to be numerous, including endocrine disorders (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal glands), dilated cardiomyopathy, arrhythmias, liver fibrosis, and cirrhosis. SCAGO noted that individuals with SCD face debilitating complications not limited to vaso-occlusive pain crisis and damage to their vital organs (including kidney and liver). According to the input received, continuous blood transfusions in patients with SCD can lead to an excessive buildup of iron, causing further organ damage and increased cancer risk. The patient input cited evidence in which patients and caregivers believed that this condition disrupted their ability to work or attend school, as well as their physical and social interactions.

Respondents reported having experience with injectable treatments (e.g., DFO) and oral treatments (e.g., DFX). They noted that DFO treatment has a demanding subcutaneous or IV administration schedule, and can be associated with important side effects, such as local irritation, high-frequency hearing loss, deafness, retinal damage, impaired vision, growth retardation, and bone abnormalities. The patient groups also reported that oral treatments are associated with improvements in quality of life, treatment adherence, patient satisfaction, and reduce preventable organ damage from iron overload. The patient input stated that improved heart and endocrine function, reduced risk of premature death, and ease of oral administration (obtained by treating patients with deferiprone) are goals that will be meaningful to patients and their families. The patient groups conclude that expanding access to appropriate iron chelation therapies such as deferiprone is vital to effectively improve patient outcomes.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert consulted by CADTH identified that the goal of treatments for patients with transfusional iron overload are to reduce hepatic iron to a safe level that will not lead to cirrhosis and hepatocellular carcinoma, while minimizing or avoiding drug-related toxicity. Cardiac iron overload is uncommon in patients with SCD.

The clinical expert indicated that challenges with existing treatments, DFX and DFO, include drug toxicity and nonadherence. DFX is contraindicated for patients with renal impairment. DFO via the IV route, can be a suitable option for a select group of patients who are motivated and have an existing indwelling catheter; however, even under these circumstances it can be challenging to maintain for a prolonged period. Risk of recurrent thrombosis or line-related infections are also present with IV DFO. Overnight SC DFO infusion is even harder to maintain over the medium to long term.

According to the clinical expert, patients most suitable for treatment with deferiprone include those with sickle nephropathy, poor IV access, adverse events (AEs) with DFO or DFX, and normal liver enzymes. Patients for whom deferiprone may not be suitable or who may require closer monitoring due to the risk of mild and severe neutropenia include those with baseline neutropenia or concomitant therapy with hydroxyurea. Patients with very severe hepatic iron overload may also be less suitable or require dosing at the upper end of the dose range for efficacy.

In routine clinical practice, the clinical expert indicated that deferiprone may be administered until LIC levels are an acceptable threshold, not a fixed duration of 12 months. The goal of therapy is to reduce and then maintain liver iron at an acceptable range of 2 to 5 mg/g dw. Deferiprone should be discontinued when iron stores have reached target range and there is no ongoing iron loading, during pregnancy and lactation and in the presence of clinically significant toxicity that cannot be safely managed with a reduction in dose.

Clinician Group Input

The input provided by 1 clinician group, Canadian Hemoglobinopathy Association (CanHaem), generally aligned with the input provided by the clinical expert consulted by CADTH. The input from CanHaem noted that there are currently 2 treatments available for transfusional iron overload: DFO (subcutaneous [SC] or IV infusion) or DFX (oral). The clinician group noted that not all patients will adequately respond to the currently available treatments and that many patients experience side effects with iron chelators; hence, additional treatment options would be beneficial for patients.

Renal dysfunction was highlighted as a common complication in patients with SCD and consequently some patients may experience intolerance to DFX. For others, the SC or IV administration of DFO may not be a feasible treatment option. The clinician group highlighted the unmet need for treatments that are better tolerated and that can improve compliance and patient convenience. In terms of place in therapy, CanHaem noted that deferiprone would be suitable for patients with SCD who demonstrate transfusional iron overload, particularly those who are unable to tolerate SC or IV drug infusion, those with liver or kidney dysfunction, and those who are not considered to be at risk of neutropenia. A clinically meaningful response to treatment was defined by the group as the maintenance or decrease of iron burden over time. CanHaem indicated that patients receiving treatment with deferiprone should be under the care of a pediatric or adult hematologist, as appropriate.

Drug Program Input

The clinical experts consulted by CADTH 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	
Would DFX (Jadenu/Exjade and generics), the other oral iron chelator therapy, have been a better comparator than the SC product DFO in FIRST and FIRST-EXT?	CDEC and the clinical expert consulted by CADTH agreed that DFX would have been a better comparator than the DFO (SC) in the FIRST and FIRST-EXT studies. However, it was noted that DFX was not approved for use as a first-line therapy for the management of transfusional iron overload in patients with SCD at the time the FIRST trial was designed.
Considerations for continuation or renewal of therapy	
Is there a response with SF, LIC, and/or CIC that would support continuation (or discontinuation) of therapy?	CDEC agreed with the clinical expert that appropriate reimbursement criteria to support renewal of deferiprone would be reduction in absolute or maintenance of low LIC, CIC, or SF concentrations.
Are there other considerations that could be used to evaluate whether therapy should be continued or renewed?	The clinical expert consulted by CADTH noted that other considerations used to evaluate whether therapy should be continued or renewed may include the presence of clinically significant AEs or SAEs and unanticipated gaps in medication use (e.g., illness and pregnancy). CDEC agreed with the input from the clinical expert.
Considerations for prescribing of therapy	
Is adherence to deferiprone an issue due to its pill burden and/or frequency of administration?	The clinical expert consulted by CADTH noted that adherence may be a challenge when the daily dose is administered TID. CDEC acknowledged the input from the clinical expert, but noted that there were no clinical data within the sponsor's application regarding differences in patient adherence to deferiprone vs. DFX.
Is there any experience giving the total daily dose of deferiprone twice a day rather than 3 times a day? If so, has this been successful in your practice?	The clinical expert consulted by CADTH noted that there is clinical experience providing the total daily dose of deferiprone BID rather than TID. The BID regimen can be associated with greater convenience for patients and improved adherence to the treatment. CDEC acknowledged the input from the clinical expert but noted that a revised dosage regimen from TID to BID is not reflective of the dosage recommended in the product monograph and there was no evidence in the submission to evaluate the effectiveness of the alternative regimen.
Care provision issues	
Are there any concerns with continuing to limit coverage of deferiprone to hematologists? Are there other specialties that should be able to obtain coverage/use deferiprone?	The clinical expert consulted by CADTH identified the concern of timely access to a pediatric or adult hematologist if coverage of deferiprone is continued to be limited to hematologists. The clinical expert added that there is not usually an urgent need for chelation for SCD and most SCD clinics would prioritize based on clinical need. The clinical expert indicated that other providers or specialists should not direct care (i.e., the initial decision or request) but could act with support from hematologists. CDEC acknowledged the input from the clinical expert.
Is combination chelation therapy used in clinical practice? If so, how often and is it effective?	The clinical expert noted that combination chelation therapy is used in Canadian clinical practice. CDEC acknowledged the input from the clinical expert and noted that was no clinical evidence for the use of deferiprone in combination with other iron chelation identified in the CADTH review.

Implementation issues	Response
Is weekly blood work a significant burden for patients and clinicians with this life-long therapy? Are there any scenarios where the frequency of monitoring maybe reduced? For example, if a patient was treated with deferiprone for a number of years without any AEs?	The clinical expert consulted by CADTH noted that weekly CBC counts would be extremely burdensome for patients and caregivers and are unlikely to be performed in routine clinical practice for patients receiving longer-term treatment with deferiprone. The clinical expert added that patients with SCD who are receiving regular transfusions or are receiving hydroxyurea medication are also getting their CBC counts monitored at each visit. The clinical expert indicated that in routine clinical practice, clinics may encourage weekly monitoring of CBC for the first 6 months of treatment, and thereafter it may be as often as their transfusions occur. The expert noted that patients and caregivers would be educated about the signs and symptoms of febrile neutropenia; instructed when to seek medical attention and to ensure that the health care provider is aware that they are receiving medication that poses a risk of neutropenia (e.g., by presenting the wallet card that is provided with deferiprone). CDEC noted that this implementation consideration is related to the clinical management of patients and outside the scope of the CADTH reimbursement recommendation for deferiprone.
How often are SF, LIC and CIC monitored in routine clinical practice for patients with SCD? Are other labs or diagnostic tests required that were not mentioned by the sponsor?	The clinical expert consulted by CADTH noted that LIC is measured yearly, with some variation depending on the degree of iron overload, either plus or minus 6 to 12 months. The SF is measured every month if patients are being treated with DFO, otherwise it is measured every 3 months. CIC may be checked at baseline and only repeated intermittently as cardiac iron overload is uncommon with patients who have SCD. According to the clinical expert, LIC, CIC, and SF concentration would be the only tests conducted to assess efficacy in this population. With respect to the monitoring of zinc levels, the expert indicated there is variation across routine clinical practice. CDEC noted that this implementation consideration is related to the clinical management of patients and outside the scope of the CADTH reimbursement recommendation for deferiprone.

AE = adverse event; BID = twice daily; CIC = cardiac iron concentration; CBC = complete blood count; DFO = deferoxamine; LIC = liver iron concentration; SAE = serious adverse event; SF = serum ferritin; SCD = sickle cell disease; SC = subcutaneous; TID = 3 times per day.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two studies were included in this review (FIRST [N = 213] and Calvaruso et al., 2014 [N = 60]). FIRST was a pivotal, late-phase (phase IV in the US, phase IIIb in other countries), multicentre, randomized, open-label, noninferiority study comparing the efficacy and safety of the iron chelator deferiprone versus DFO in patients with SCD or other transfusion-dependent anemias (N = 213). Eligible patients were randomized (2:1) to receive either deferiprone or DFO for up to 12 months. Randomization was stratified by disease category (SCD versus other anemias) and burden of transfusional iron loading in the 3 months before baseline (≤ 0.3 mg/kg/day versus > 0.3 mg/kg/day). The mean age for patients was 16.9 years (SD = 9.6). The primary

end point of the study was change from baseline in LIC after 12 months. For noninferiority, the upper limit of the 96.01% CI could be no more than 2 mg/g dw. Secondary outcomes included changes in cardiac iron concentration (CIC), SF, and health-related quality of life (HRQoL). For CIC and for SF, if the 96.01% CI contained zero (0) then no significant difference between the 2 treatment groups was assumed. The mean age was 16.9 years. Most patients were white (77.2%) and 46.5% had no prior chelation therapy.

The second study was conducted by Calvaruso et al. (2014), a 5-year multicentre open-label randomized controlled trial (RCT) to compare the safety and efficacy of deferiprone versus DFO in Italian patients. Eligible patients were randomized (1:1) to receive either deferiprone or DFO for up to 12 months. The primary outcome was a reduction in SF and patients were considered responders if their SF values < 400 ng/mL. Patients were randomized consecutively after confirming eligibility, no stratification was conducted. Baseline characteristics for race and prior chelation therapy were not provided, though the mean age ranged from 36.4 to 35.8 years (SD = 13.9 to 11.6).

Efficacy Results

Liver Iron Concentration

In the FIRST trial, the analysis of covariance (ANCOVA) model, the mean change from baseline was similar between the 2 treatment groups (−4.13 for deferiprone versus −4.38 for DFO) and the upper limit of the 96.01% CI was 1.48, thereby supporting the noninferiority criterion. Subgroup analyses of SCD versus other anemias were generally supportive of the main analysis but sample sizes were too small for any definitive conclusions.

Cardiac Iron Concentration

In the FIRST trial, changes in CIC values were generally supportive of the primary end point. The least squares mean (LSM) of change in log-transformed cardiac MRI T2* (ms) difference between both groups was −0.000295 ± 0.026134 (96.01% CI, −0.054247 to 0.053657); thereby supporting noninferiority of deferiprone to DFO.

Serum Ferritin

In the FIRST trial, changes in SF values were generally supportive of the primary end point. LSM difference (deferiprone minus DFO) was 375.07 ± 308.62 (96.01% CI, −260.63 to 1,010.76); thereby supporting noninferiority of deferiprone to DFO. In the Calvaruso et al. study, 36.6% of patients in the deferiprone group and 3.3% of patients in the DFO groups were responders. The changes over time in SF in deferiprone versus DFO patients (as per linear effects model) were statistically not significant, moreover the study's sample size was too small for any definitive conclusions.

Harms Results

In the FIRST trial, at least 1 AE was reported for 88.2% of patients in the deferiprone group and 88.2% of patients in the DFO group. The most frequently reported AE was pyrexia (28.3% of deferiprone patients versus 32.9% of DFO patients), followed by abdominal pain (25.0% of deferiprone patients versus 13.2% of DFO patients). Patients in the deferiprone group had higher rates of liver enzyme increases. The number of patients reporting agranulocytosis and neutropenia in both groups was low.

Critical Appraisal

There were concerns in the FIRST trial for internal validity. Although the trial was open label, most of the outcome measures were objective and relied on a central laboratory; thereby indicating a low risk of detection bias. On the other hand, nonobjective outcomes (e.g., HRQoL and subjective AEs) could be affected by the lack of blinding. Randomization and allocation were conducted by an electronic system, suggesting that the risk of bias due to the randomization process was probably low. Per the clinical expert consulted by CADTH, the noninferiority margin used in FIRST was clinically appropriate. A high rate of protocol deviations and loss to follow up occurred in FIRST, which may create some uncertainty in the data as it increases bias toward the null and falsely declaring noninferiority. The sensitivity analyses also did not support noninferiority of deferiprone to DFO. Investigators used both an intention-to-treat (ITT) set, and per-protocol set for efficacy analyses; however, a true ITT was not conducted.

There were concerns in the FIRST trial for external validity. The eligibility criteria and baseline characteristics were generally representative of the Canadian patient population, with a few notable exceptions (e.g., race). Baseline LIC of 7 mg/g dw was used in the inclusion criteria of the trial however in practice, patients with LIC lower than 7 mg/g dw would be treated. Patients treated with hydroxyurea within 30 days were excluded; however, these patients would not be excluded in routine practice and often, hydroxyurea is a concomitant medication. Majority of the patients were white and prior chelation therapy with DFO was higher than what would be expected in routine clinical practice. Efficacy and harms outcomes used in FIRST were generally clinically meaningful and important to clinicians and patients. As noted by the clinical expert, few patients with SCD have cardiac iron overload in routine clinical practice so this measure is not used as much as LIC. SF concentrations are somewhat unreliable in routine clinical practice because many factors affect these values outside of iron overload. Furthermore, there were concerns with the high discontinuation rates in the study.

In the Calvaruso et al. (2014) study, the investigators adequately used randomization and allocation concealment in the study and provided rationale for why blinding was unfeasible. The use of SF as the only efficacy end point was a major limitation of the study, as this end point is not typically used in isolation to evaluate response to iron chelation in Canada. There were major concerns about generalizability to Canadian clinical practice in this study. With respect to the eligibility criteria, the study excluded patients with white blood cell counts less than 3, which may prevent Black patients and patients on hydroxyurea from accessing treatment (populations for which this drug would be used for in routine clinical practice) because these populations typically have white blood cell counts that are lower. Per the clinical expert consulted by CADTH, the baseline transfusion burden appeared to be low in the trial; whereas in routine clinical practice patients with higher transfusion burden would be treated. For the baseline SF values, the clinical expert indicated they are low compared to what would be expected in routine clinical practice, suggesting patients participating in the trial may be less iron overloaded than typically seen.

Indirect Comparisons

Description of Studies

In the absence of direct comparative evidence from trials, the aim of the NMA conducted was to compare the relative efficacy of deferiprone versus DFX and DFO. The sponsor chose to restrict the NMA to the 2 RCTs. FIRST was a late-phase (IIb/IV), open-label, noninferiority

trial comparing deferiprone with DFO in patients with SCD or anemias with transfusional iron overload, while the NCT00067080 was a phase II open-label trial comparing DFX with DFO in patients with SCD with transfusional iron overload. The mean duration of follow-up was 12 months in the FIRST trial, and 13 months in the NCT00067080 trial. The inclusion and exclusion criteria were similar with some exceptions: FIRST required a higher baseline LIC values compared to NCT00067080, but excluded patients with baseline LIC exceeding 30 mg/g dw, and patients who received treatment with hydroxyurea within 30 days of the study. The NMA used a Bayesian approach using random-effects models with noninformative prior in all analyses. The clinical end points included change from baseline to 12 months in LIC and SF. The quality of the included studies was assessed by the sponsor according to the revised Cochrane risk-of-bias tool for randomized trials.

Efficacy Results

The results from the sponsor-submitted NMA suggested that in the overall population, no treatment was favoured when deferiprone was compared with DFX and DFO with respect to change from baseline to 12 months in LIC and SF. Compared to deferiprone, the mean difference for change at 12 months in LIC was −0.4 (95% CrI, −1.7 to 0.9) for DFO, and −0.7 (95% CrI, −3.6 to 2.3) for DFX. Compared to deferiprone, the mean difference for change at 12 months in SF was −364.4 (95% CrI, −961.4 to 237.2) for DFO, and + 11.2 (95% CrI, −688.2 to 712.5) for DFX.

Harms Results

No analysis of harms was included in the indirect comparisons.

Critical Appraisal

The sponsor submitted NMA was based on a systematic literature review that identified studies according to prespecified inclusion criteria. Overall, based on the methods detailed in the report, the systematic literature review has an overall adequate search strategy, screening, and appraisal of the risk of bias of the included studies. The systematic review identified 11 primary studies for inclusion, based upon preidentified study selection criteria, which were further refined on an ad hoc basis, potentially introducing selection bias. All titles, abstracts, and full texts of identified studies were screened by 2 independent reviewers, and any discrepancies were resolved by a third reviewer. The main limitations of the NMA relate to data sparseness, network structure, and potential violation of the transitivity assumption. As the network was sparse, fixed-effects models were used, and there was no opportunity to use meta-regression to adjust for variability in baseline characteristics and correct for potential bias. Furthermore, the evidence is imprecise in most of the effect estimates from the NMA, with wide credible intervals that could include an appreciable threshold of benefit or lack of benefit. Additional sensitivity analyses were not performed due to limited data.

There were some important differences between the FIRST and NCT00067080 trials that increase the uncertainty of the NMA analyses. The FIRST trial required a higher baseline LIC (> 7 mg/g dw) than NCT00067080, which indicates a more severe iron overload. The clinical expert consulted highlighted that exclusion of patients with LIC exceeding 30 mg/g dw in the FIRST trial could result in a loss of a population who are nonadherent generally to iron chelators, which is likely to bias the study results in favour of deferiprone. The baseline patient characteristics differed between the 2 trials with patients enrolled in FIRST appearing to have a more severe iron overload as evidenced by the elevated SF and LIC values at baseline, compared to patients enrolled in NCT00067080, which could bias the results. Despite the

described differences between the 2 studies, there does not appear to be evidence for a difference in treatment effects between deferiprone, DFX, and DFO with respect to change at 12 months in LIC and SF, aligning with the opinion of clinical experts consulted. The above limitations must be considered when drawing conclusions based on the results of the NMA.

Other Relevant Evidence

Description of Studies

FIRST-EXT was a 2-year, open-label, single-arm extension study conducted to evaluate the efficacy and safety of deferiprone consisting of 500 mg tablets or 80 mg/mL oral solution for the treatment of patients with transfusional iron overload due to SCD or other anemias. A total of 134 patients from the FIRST enrolled into the FIRST-EXT extension study.

Efficacy Results

The mean (SD) change from baseline to year 1, year 2, and year 3 in LICs were supportive of results from the FIRST.

Harms Results

Harms were similar to AEs reported in FIRST. A total of 104 (77.6%) patients reported AEs, with the most common being pyrexia (26.1%), bone pain (26.1%), abdominal pain (19.4%), and sickle cell crisis (18.7%) which were also reported in the pivotal trial. A total of 13 (9.7%) of patients experienced SAEs that were considered related to the study drug, including neutropenia (9.0%), agranulocytosis (1.5%), thrombocytopenia (0.7%), and generalized edema (0.7%). Severe cases of sickle cell crisis were reported in 13 patients (9.7%), severe cases of pyrexia in 5 (3.7%), severe cases of abdominal pain in 3 (2.2%), and severe cases of agranulocytosis, cholecystectomy, pneumonia, increased alanine transaminase (ALT), increased aspartate aminotransferase (AST), and decreased neutrophil count in 2 each (1.5%).

Critical Appraisal

Limitations of the extension study include the absence of an active comparator and the fact that potential confounders were not accounted for, which limits causal conclusions. Interpretation of some outcomes were also limited by the large amount of missing data due to attrition. Subgroup analyses were descriptive and often limited to few patients reducing the chance of detecting a true effect. As the extension study consisted of patients who took part in the pivotal FIRST parent study, it is reasonable to expect that the same limitations related to generalizability apply to the extension study.

Other Considerations

The FIRST trial was not designed or powered to evaluate potential differences in renal toxicity associated with deferiprone compared with DFO. To support claims used in the economic evaluation that deferiprone has a superior renal AE profile compared with DFO, the sponsor included an unpublished comparison of eGFR values in deferiprone-treated patients from the FIRST-EXT trial against DFO- and DFX-treated patients obtained from a real-world dataset obtained from the US electronic medical records (EMR). CADTH identified limitations with the unpublished data that precluded any conclusions regarding the comparative safety of these drugs, including heterogeneity in treatment setting (e.g., within the setting of a phase III clinical trial versus real-world data), generalizability concerns regarding the use of EMR

data from the US with the management of SCD patients in Canadian practice, and significant loss to follow-up. In addition, the clinical expert noted that eGFR values would not be used in isolation within Canadian practice to inform treatment decisions (e.g., proteinuria would also be evaluated). The clinical expert consulted by CADTH noted that both DFO and DFX can pose a risk for renal toxicity, and it was plausible that deferiprone may pose a lower risk for renal toxicity; however, the available evidence is insufficient to draw any conclusions regarding the magnitude and clinical relevance of any potential differences across the treatments for patients with no known contraindications.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target populations	People with SCD or other anemias who have transfusional iron overload
Treatment	Deferiprone
Dose regimen	The recommended dosage is 25 to 33 mg/kg body weight, orally, TID for a total daily dose of 75 mg/kg to 100 mg/kg body weight.
Submitted price	Deferiprone, tablet 1,000 mg: $33.47 Deferiprone, oral solution 100 mg/mL: $3.35 per mL
Treatment cost	At the total daily dose of 75 mg/kg to 100 mg/kg body weight, the monthly cost ranges from $6,113 to $8,151. Drug wastage was included.
Comparators	DFO DFX
Perspective	Canadian publicly funded health care payer
Outcome(s)	QALYs
Time horizon	Lifetime (62.5 years)
Key data source	FIRST trial and the sponsor's indirect comparison were used to support the assumption of equivalent efficacy deferiprone vs. DFX and DFO. Real-world US medical records (TriNetX): changes patients' in eGFR overtime
Key limitations	• The sponsor assumed equivalent clinical efficacy of deferiprone compared to DFO or DFX – i.e., all treatments are equally effective at chelating iron in patients with SCD and other anemias with transfusional iron overload. This assumption of equivalence is associated with uncertainty, given the limitations with the indirect comparison, but plausible according to clinical expert feedback obtained by CADTH. • The sponsor assumed patients receiving deferiprone experienced a slower decline in renal function compared to DFO or DFX. CADTH reviewed the real-world evidence and noted that evidence provided by the sponsor was insufficient to draw to conclusions on this claim. Clinical expert feedback noted that the this may be plausible, but there is no robust evidence supporting this assumption, and as such, assumption was highly uncertain.

Component	Description
	• The sponsor's 3-health state Markov model is insufficient to capture the care pathway and may incorrectly estimate the total costs and QALYs of patients with SCD or other anemias. The sponsor's model also did not allow patients who failed the first iron chelation therapy (ICT) to receive subsequent drugs for ICT; this assumption did not align with clinical practice based on feedback from the clinical expert consulted by CADTH, and overestimated any benefits associated with decline in renal function attributed to deferiprone. • The sponsor's economic model did not consider all relevant comparators for patients with SCD or other anemias receiving chronic transfusion. Patients may receive multiple drugs for ICT, or exchange transfusion which negates the need for ICT. The model was not flexible to assess the cost-effectiveness of deferiprone in these situations. • The sponsor's assumption regarding ICT discontinuation due to causes other than renal impairment was not supported by any robust evidence. The clinical expert consulted by CADTH advised that the decision to stop ICT is dependent on iron burden, which can vary overtime.
CADTH reanalysis results	• CADTH revised the sponsor's model by reducing the proportion of patients on DFX receiving Exjade to 10% and the frequency of an eye test for patients on DFX to once annually; and, assuming equivalent effect on eGFR levels across drugs used for ICT. • Based on CADTH's base case, deferiprone is associated a higher cost (incremental $600,356) and improved QALYs (incremental 0.09). Given the small QALY difference and high incremental cost, this resulted in an ICER of $6,812,661 per QALY compared to DFX. DFO is dominated by DFX. • A price reduction of at least 79.5% would be needed for deferiprone to be cost-effective at a WTP threshold of $50,000 per QALY.

DFO = deferoxamine; DFX = deferasirox; ESRD = end-stage renal failure; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; QALY = quality-adjusted life-year; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: relevant comparators and treatment regimens were excluded; treatment costs were overestimated due to an overestimation of average target population weight; market share and market capture of comparator treatments were uncertain; and duration of treatment was overestimated.

CADTH undertook reanalyses which included revising the recommended dosage and drug cost of DFO, revising the average population weight to 42.5 kg, and altering market shares of DFX. Based on these changes, CADTH reanalysis reported that the reimbursement of deferiprone for the treatment of transfusional iron overload due to SCD and other anemias in adults and pediatric groups would be associated with a budgetary increase of $2,253,178 in year 1, $2,852,419 in year 2, $4,043,712 in year 3 for a 3-year total incremental cost of $9,149,309. CADTH could not address all identified limitations.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell,

Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: November 24, 2022

Regrets: One of the expert committee members did not attend

Conflicts of interest: None