CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

DEFERIPRONE
(Ferriprox — ApoPharma Inc.)
Indication: Transfusional Iron Overload due to Thalassemia

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that deferiprone be listed for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate, if the following condition is met:

Condition:
- List in a manner similar to deferasirox.

Reasons for the Recommendation:
1. Three pivotal studies suggested that treatment with deferiprone was associated with a reduction in cardiovascular events, improvements in left-ventricular ejection fraction (LVEF), and reduced rates of developing or worsening cardiac disease.
2. At the submitted price, the annual cost of treatment with deferiprone ($49,866 to $66,488 for a 60 kg patient) is similar to treatment with deferasirox ($37,165 to $74,329 for a 60 kg patient).

Of Note:
- There is a significant unmet need for the treatment of thalassemia patients who are unable to achieve adequate chelation with existing therapies, or for whom toxicity prevents the use of alternative treatment options.
- CDEC noted that individual patients may require more than one chelation medication. Due to the absence of clinical and pharmacoeconomic evidence, CDEC was unable to make a recommendation regarding the combination use of deferiprone and deferoxamine.

Background:
Thalassemia is a rare hereditary condition that affects the production of the alpha- or beta-globin chains of hemoglobin; beta-thalassemia is the prevalent subtype. Severe anemia occurs within the first two years of life in patients with beta-thalassemia major, which requires the initiation of lifelong transfusion therapy. Iron overload is inevitable in these patients due to the accumulation of iron from red blood cell transfusions and increased iron absorption secondary

to ineffective erythropoiesis. Iron chelation is the main therapy for iron overload. Deferiprone is an oral chelating drug indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The recommended dose is 25 mg/kg body weight to 33 mg/kg body weight orally, three times a day, for a total daily dose of 75 mg/kg body weight to 100 mg/kg body weight.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) and pivotal studies of deferiprone for the treatment of transfusional iron overload due to thalassemia syndromes, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with thalassemia.

Patient Input Information
One patient group, the Thalassemia Foundation of Canada, responded to the CDR call for patient input. Information was gathered from various sources, including a search of the medical literature, a collection of focus group reports, clinical practice guidelines, and other relevant materials from the Cooley's Anemia Foundation (United States), the Thalassemia International Federation, the Canadian Organization for Rare Disorders, and other organizations representing the interests of patients with thalassemia.

- Transfusion-dependent thalassemia has a significant impact on the daily life of patients and their caregivers. The iron overload that is associated with the treatment of thalassemia is a potentially fatal condition that can result in endocrine disorders, cardiomyopathy, arrhythmias, liver fibrosis, and cirrhosis.
- Patients reported having experience with injectable treatments (e.g., deferoxamine) and oral treatments (e.g., deferasirox). They noted that deferoxamine has a demanding subcutaneous or intravenous 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.
- Patients reported that oral treatments are associated with improvements in quality of life, treatment adherence, and patient satisfaction.

Clinical Trials
The CDR systematic review included five RCTs and two retrospective observational studies. Three studies were defined as pivotal: LA16 (N = 61) and two five-year observational retrospective studies (LA12 [N = 168] and Borgna-Pignatti 2006 [N = 516]). The non-pivotal studies included one two-year Canadian RCT (LA01) (N = 71) and three Italian RCTs (Calvaruso 2015 [N = 88], Maggio 2009 [N = 213], and Maggio 2002 [N = 144]). Calvaruso 2015 included thalassemia intermedia patients, while all other studies included patients with thalassemia major. None of the included studies enrolled patients who were experiencing inadequate control with their current therapy. Maggio 2009 was the only study that compared deferiprone with the sequential use of deferiprone and deferoxamine (deferiprone-deferoxamine); all other studies compared deferiprone with deferoxamine alone.

In all included studies except Calvaruso 2015, the mean age of patients ranged from 17 years (Borgna-Pignatti 2006) to 26 years (LA16); the mean age in Calvaruso 2015 was 41 years. In the pivotal observational study LA12, the patients in the deferiprone group were significantly younger at the start of their first chelation therapy than patients in the deferoxamine group (4.5

years versus 6.8 years) and at the start of the study (17.1 years versus 19.4 years). The mean serum ferritin concentration (SFC) ranged from 1,122 mcg/L (Calvaruso 2015) to 2,795 mcg/L (LA16). In the pivotal study (LA16), patients randomized to the deferiprone group had statistically significantly lower SFC (1,791 mcg/L) than those in the deferoxamine group (2,795 mcg/L). The dry liver weight iron concentration ranged from 3.36 mg/g (Maggio 2002) to 9.15 mg/g (LA01). In the observational study LA12, liver iron concentration (LIC) was reported in wet weight, and it was statistically significantly higher in those in the deferiprone group (1.6 mg/g) than in those in deferoxamine group (0.9 mg/g).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Five-year mortality rates
- Treatment failure — defined by an increase in ferritin levels more than 1,000 mcg/L
- Cardiac disease-free survival
- Change from baseline in LVEF
- Changes in cardiac iron concentration as measured by magnetic resonance imaging (MRI)
- LIC
- Serum ferritin
- RAND 36-Item Health Survey (RAND 36) — a questionnaire composed of eight domains: physical functioning (10 items), role physical (four items), pain index (two items), general health (five items), energy/fatigue (four items), social functioning (two items), role emotional (three items) and emotional well-being (five items)
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Efficacy

- There was no statistically significant difference between deferiprone and deferoxamine in five-year mortality rates:
  - Calvaruso 2015: 4.0% with deferiprone versus 9.8% with deferoxamine; *P* = 0.360
  - Maggio 2009: 3.7% with deferiprone versus 1.9% with deferoxamine; *P* = 0.32.
- Treatment failure occurred at a higher rate in the deferiprone group compared with the deferiprone-deferoxamine group (7.4% versus 1.9%) in Maggio 2009, while in Maggio 2002 there was only one treatment failure reported in each of deferiprone and deferoxamine groups. The differences between groups were not statistically significant.
- Deferiprone was associated with significantly lower rates of cardiac events than deferoxamine:
  - LA12: 5% versus 19%; *P* = 0.003
  - Borgna-Pignatti: 0% versus 15%; *P* not reported.
- Differences in change from baseline in LVEF between deferiprone and deferoxamine were not consistent across LA16, Maggio 2002, and LA01. In LA16, deferiprone-treated patients demonstrated a statistically significant improvement in LVEF compared with deferoxamine-treated patients (3.07% versus 0.32%). In contrast, there was no statistically significant difference between deferiprone and deferoxamine in Maggio 2002 (0% versus 1%) and LA01 (17.3% versus 1.9%).The mean differences in LVEF for deferiprone versus deferoxamine at one year were:
  - LA16: 2.8 (95% CI [confidence interval], 1.0 to 4.6); *P* = 0.0034
  - LA01: 4.9 (95% CI, −0.53 to 10.3); *P* = 0.54
  - Maggio 2002: −1.0 (95% CI, −3.3 to 1.3); *P* not reported.

- Deferiprone-treated patients demonstrated a statistically significant reduction in myocardial iron concentration at one year compared with deferoxamine-treated patients (27% versus 13%, *P* = 0.0228) in LA16; however, there was no statistically significant difference between deferiprone and deferoxamine in Maggio 2009 at five years.
- Studies LA16, LA01, and Maggio 2002 demonstrated no statistically significant differences between deferiprone and deferoxamine for change from baseline in LIC at one and two years. Results in Study LA12 were inconsistent at one, two, and five years. Mean (standard deviation [SD]) changes from baseline for deferiprone versus deferoxamine were:
  - LA16: −0.93 mcg/g (2.9) versus −1.54 mcg/g (2.5) at one year (*P* = 0.3961)
  - LA01: 0.36 mcg/g (4.9) versus 0.69 mcg/g (3.4) at two years (*P* = 0.8426)
  - Maggio 2002: 1.02 mcg/g (3.5) versus 0.35 mcg/g (0.5) at one year (*P* > 0.05)
  - LA12: 2.1 mcg/g (1.1) versus 2.2 mcg/g (2.3) at one year (*P* = 0.906); 1.9 mcg/g (0.9) versus 1.3 mcg/g (0.6) at two years (*P* = 0.0151); and 2.8 mcg/g (1.1) versus 2.2 mcg/g (1.0) at five years (*P* = 0.055).
- Borgna-Pignatti 2006 reported a statistically significant difference in serum ferritin favouring deferoxamine compared with deferiprone (*P* < 0.001); however, none of the other studies demonstrated a significant difference between these two treatments.
- Study LA16 showed that there were no differences between deferiprone and deferoxamine in all domains of RAND 36, with the exception of emotional role, where deferiprone was associated with a statistically significant improvement from baseline, while deferoxamine was associated with worsening from baseline (1.2 versus −11.1; *P* = 0.049).

Harms (Safety and Tolerability)

- The proportion of patients who withdrew as a result of adverse events was greater in the deferiprone groups (range 6.9% to 29.3%) than in the deferoxamine treatment groups (range 0% to 7%).
- Adverse events were reported at higher rates in deferiprone-treated patients compared with deferoxamine and included nausea, eructation, increased aspartate aminotransferase, electrocardiogram T-wave inversion, and increased appetite (all > 5% more frequent).
- Leukopenia, neutropenia, or agranulocytosis occurred at higher rates in deferiprone-treated patients (2.8% to 15.9%) versus deferoxamine (0% to 2.8%).
- A total of eight patients treated with deferiprone and 34 patients treated with deferoxamine died during the included studies.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing deferiprone with deferasirox for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The submitted three-state Markov model was adapted from a previously published model that compared deferiprone alone with other iron chelators from the UK National Health Service perspective. The manufacturer used this model to capture differences in mortality, morbidity, quality of life, and resource use over a five-year time horizon (with annual cycles) from the perspective of the Canadian publicly funded health care system. As efficacy data were not available to compare deferiprone with deferasirox, efficacy parameters were taken from studies comparing deferiprone with deferoxamine. Data on adverse events were sourced from the product monographs of deferiprone and deferasirox. Utility and disutility values were sourced from published literature. Drug acquisition costs for each treatment were obtained from the manufacturer and the Ontario Ministry of Health and Long-Term Care. Costs for adverse events were derived from UK data sources and converted to

Canadian values. Monitoring costs were obtained from the Ontario Schedule of Benefits. The manufacturer reported that deferiprone dominated (i.e., it was less costly and more effective) deferasirox.

CDR identified several limitations with the manufacturer's analysis; however, the primary issue was that the manufacturer did not consider all of the appropriate comparators — deferoxamine in combination with deferiprone was not included as a comparator in the analysis. Other limitations were as follows:

- The absence of comparative data on the efficacy of deferiprone versus deferasirox required the assumption that efficacy data for deferoxamine can be used as a proxy for deferasirox, which imparted substantial uncertainty to the efficacy inputs. CDR therefore tested the assumption of no difference in efficacy.
- The manufacturer's economic analysis did not consider different doses for deferasirox and deferiprone. CDR undertook reanalyses using various doses.
- The rates of adverse events used in the analysis and the generalizability of the UK costs associated with adverse events were associated with some uncertainty, and monitoring costs may have been overestimated. CDR undertook reanalyses with revised rates and costs where relevant data were available.

When varied independently, only changes to dose (deferiprone 75 mg/kg/day compared with deferasirox 20 mg/kg/day, or deferiprone 100 mg/kg/day compared with deferasirox 30 mg/kg/day) altered the direction of the results in comparison with the manufacturer's base case. When comparative doses recommended by the CDR clinical expert were applied (for patients with lower iron burden: deferiprone monotherapy 75 mg/kg/day versus deferasirox monotherapy 30 mg/kg/day; for patients with higher iron burden: deferiprone monotherapy 100 mg/kg/day versus deferasirox monotherapy 40 mg/kg/day) along with an assumption of equivalent efficacy for deferiprone and deferasirox, deferiprone still dominated deferasirox. However, when adverse event rates were revised in the model, the small quality-adjusted life-year (QALY) benefit associated with deferiprone compared with deferasirox was lost.

It was not possible for CDR to compare deferiprone monotherapy with deferoxamine in combination with deferiprone due to the lack of appropriate evidence comparing these treatments on the outcomes of interest.

At the recommended dose of 25 mg/kg body weight to 33 mg/kg body weight three times a day (75 mg/kg body weight to 100 mg/kg body weight per day), the annual cost of deferiprone ranges from $49,866 to $66,488 for a 60 kg patient. The annual cost of deferasirox for a 60 kg patient is $37,165 for a daily dose of 20 mg/kg body weight, $55,747 for a daily dose of 30 mg/kg body weight, and $74,329 for a daily dose of 40 mg/kg body weight. The annual cost of deferoxamine for a 60 kg patient, based on a daily dose range of 35 mg/kg body weight to 50 mg/kg body weight ranges from $7,447 to $11,153 for the generic option and from $20,998 to $31,641 for the branded option.

Discussion Points:

CDEC noted the following:

- Deferiprone is associated with significant toxicity, including clinically important changes to neutrophil populations. The impact of this toxicity is mitigated by the reversible nature of the changes, and the existence of a clinical monitoring and access program.

- None of the included studies explicitly defined inadequate chelation as identified in the Health Canada indication.
- Dosing of deferiprone was variable across the studies and may not correspond to clinical practice in Canada.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no direct or indirect comparisons of deferiprone with deferasirox, the alternative available oral chelation agent.
- The efficacy and safety of deferiprone in pediatric patients requires further evaluation.
- There are limited data demonstrating the impact of deferiprone on the quality of life of patients compared with alternative treatments.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

February 17, 2016 Meeting:

Regrets:

Three CDEC members were unable to attend the meeting.

Conflicts of Interest:

None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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