Common Drug Review
Patient Group Input Submissions

deferiprone (Ferriprox) for transfusional iron overload

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.
Thalassemia Foundation of Canada — permission granted to post.

CADTH received patient group input for this review on or before October 16, 2015.
The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

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Thalassemia Foundation of Canada

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Ferriprox (deferiprone) for transfusional iron overload
Name of the patient group		Thalassemia Foundation of Canada
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1.1 Submitting Organization

The Thalassemia Foundation of Canada is a national not-for-profit organization that provides education and support to Canadians living with thalassemia syndromes. Originally founded as a support group for patients and their parents, it has grown over the years to encompass fundraising for medical research, patient outreach programs, and participation in the Thalassemia International Federation (TIF) as well as national and international advisory committees and conferences. Its mission statement is: "To support and fund thalassemia scientific research, treatment, patient services, public awareness, and education."

1.2 Conflict of Interest Declarations

a) ApoPharma and Novartis are the two main pharmaceutical companies that provide donations to the Thalassemia Foundation of Canada for educational material and other important initiatives.

b) Preparation of this submission was supported by the Thalassemia Foundation of Canada.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

Information for this section was gathered through a search of the medical literature (PubMed), as well as collection of focus group reports, clinical practice guidelines, and other relevant materials from the Cooley's Anemia Foundation (US), the Thalassemia International Federation, the Canadian Organization for Rare Disorders, and other organizations representing the interests of patients with thalassemia.

2.2 Impact of Condition on Patients

<u>Basics of thalassemias and iron overload</u>

The thalassemia syndromes are a group of hereditary blood disorders that involve varying degrees of anemia due to alterations in the natural structure and function of the hemoglobin molecule. Thalassemias are broadly divided into transfusion-dependent syndromes, in which patients require

regular blood transfusions over their lifetimes, and transfusion-independent ones, in which the anemia is not severe enough to require regular transfusion (Thalassemia Foundation of Canada Guidelines, 2013). This report will focus on transfusion-dependent thalassemias, of which β-thalassemia major is the most common.

While regular blood transfusions are necessary to sustain life in patients with transfusion-dependent thalassemias, the transfused blood carries with it a larger amount of iron than the recipient's body is able to fully process or eliminate. With regular transfusions over an extended period of time, this excess iron builds up in target tissues including the liver, heart, and endocrine organs, a condition known as iron overload (Cappellini TIF Guidelines, 2014). This process can be slowed or reversed through the use of iron chelators, pharmaceutical agents that bind to iron and allow its excretion from the body. Three iron chelators are currently available (deferoxamine, deferasirox, and deferiprone); their effects will be described in more detail in sections 2.3 and 3.2.

Consequences for patients

Because excess iron is stored in several different organs and tissues within the body, the consequences of iron overload are many and varied; they may include endocrine disorders (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly the adrenal glands), dilated cardiomyopathy, arrhythmias, liver fibrosis, and cirrhosis (Cappellini TIF Guidelines, 2014). If left untreated, transfusional iron overload is usually fatal in early adulthood, most often due to iron buildup in the myocardium and consequent heart dysfunction (Borgna-Pignatti Haematologica 2004).

The most comprehensive evaluation of the burden of transfusion-dependent thalassemia and associated iron overload comes from a study that surveyed the experiences of almost 2000 patients and caregivers across 10 countries (Caro Acta Haematol 2002). As the survey was conducted in 1999 and 2000, the chelating agent used for most patients was deferoxamine, the only option available in many markets at the time. Even with deferoxamine chelation, patients and caregivers reported significant impacts of thalassemia and transfusions on their quality of life:

- Patients of all ages reported significant disruptions to their ability to work or attend school, with an average of 2-3 missed days per month; absences were even higher among patients with iron-related cardiac or liver disease. Many adult patients reported not being able to work at all due to their disease, its complications, and its treatment
- A majority of pediatric patients reported frequent disruptions to their physical activity level, family activities, interactions with friends, and ability to keep up with schoolwork
- A majority of patients in all age groups believed that they would be able to have a better personal/social life if they did not have thalassemia and/or did not have to undergo deferoxamine treatment
- One in five adult respondents felt that it was not appropriate for them to have children, given the demands of the disease on them personally as well as the risk of their children inheriting the syndrome

2.3 Patients' Experiences With Current Therapy

In Canada and most markets worldwide, there are now three options for chelators to treat iron overload in transfusion-dependent thalassemia patients – deferoxamine, deferasirox, and deferiprone.

Deferoxamine

Deferoxamine was introduced in the 1970s and for many years was the only available option for iron chelation. Its ability to reduce the body's iron stores – particularly the iron contained in the liver and bound to ferritin in the bloodstream – greatly improved patient survival compared with the pre-chelation era (Borgna-Pignatti Haematologica 2004). However, its ability to remove iron from the heart is limited, and roughly two-thirds of transfusion-dependent thalassemia patients maintained on deferoxamine-only chelation will develop a significant level of cardiac iron overload (Tanner JCMR 2006). Deferoxamine also has a demanding administration schedule – it must be infused subcutaneously or intravenously over a period of 8-12 hours, 5-7 times per week (usually overnight) (Desferal Product Monograph). This administration schedule is a significant barrier to patients' willingness to follow their chelation regimen as prescribed. Many patients also experience side effects including local irritation at the site of infusion, high-frequency hearing loss, deafness, retinal damage with impaired vision, growth retardation, and bone abnormalities (Desferal Product Monograph), which can further impair their desire to continue with deferoxamine treatment (Ward BMC Clin Pharmacol 2002).

Deferasirox

To address the compliance challenges associated with parenteral administration of deferoxamine, the previous standard of care, two orally active iron chelators were introduced in many markets in the late 1990s/early 2000s – deferasirox (discussed below) and deferiprone (discussed in section 3).

Deferasirox is a once-daily tablet that is crushed and mixed in with liquids or foods (Exjade Product Monograph). In terms of effect on serum ferritin and liver iron, its efficacy appears to be equivalent to that of deferoxamine (Exjade Product Monograph). Deferasirox may have some efficacy in clearing iron from the heart in patients with mild to moderate, but not severe, total body iron load; however, there appears to be little significant impact on cardiac function and the effects on survival are unknown (Wood Am J Hematol 2010, Wood Blood 2010). The safety profile of deferasirox is still evolving, and warnings about the risk of kidney failure, liver failure, and gastrointestinal hemorrhage, sometimes fatal, have been added to its label (Exjade Product Monograph). Patients switching off deferoxamine and onto deferasirox have reported significant improvements in quality of life, treatment adherence, and satisfaction with their therapy; these may be related to the less demanding oral route of administration and lack of injection-site adverse events (Porter Anemia 2012).

Limitations of current options

While the availability of oral chelators has addressed some of the patient adherence concerns associated with deferoxamine, non-compliance remains an important issue. In a recent series of focus groups conducted by the Cooley's Anemia Foundation, patients and parents of young patients identified several important barriers to treatment adherence, including injection-site reactions and other adverse events with deferoxamine, and dislike of the taste/texture of deferasirox. Respondents in these focus groups reported that the availability of oral chelators has improved their adherence to treatment and overall quality of life compared with 5 years ago; they felt that further improvements could happen if additional oral treatment options were available. (CAF Focus Groups Report 2015)

2.4 Impact on Caregivers

Since thalassemia is a condition that manifests in early infancy, the burden of daily care in the early years often falls on the patient's parents, who may themselves suffer from a thalassemia syndrome. Parents will need to spend significant amounts of time and effort taking their child to the clinic for transfusions, and supporting their child's use of the prescribed chelation regimen. This can be

particularly challenging if deferoxamine is used, since parents will likely have to assist with setting up the overnight infusion, and also with encouraging their children to accept the demands of its administration.

Although the risk of iron-related clinical complications increases with patient age and the cumulative number of lifetime transfusions, iron-related cardiac, endocrine, and liver disease can develop even in very young patients. In the previously mentioned multi-country survey of patients treated primarily with deferoxamine, 11% of patients under age 10 had at least one iron-related complication; this rose to 29% for patients aged 10 to 18. In both age cohorts, iron-related organ dysfunction was linked to significantly more absences from school and limitations to physical, family and social activities, placing an additional burden on parents/caregivers as well as on the patients themselves (Caro Acta Haematol 2002).

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information for this section was gathered through a search of the medical literature (PubMed), as well as collection of focus group reports, clinical practice guidelines, and other relevant materials from the Cooley's Anemia Foundation (US), the Thalassemia International Federation, the Canadian Organization for Rare Disorders, and other organizations representing the interests of patients with thalassemia.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

Deferiprone (Ferriprox) is indicated in Canada for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. While deferiprone is a recent addition to the Canadian market, it has been approved and used in many other countries worldwide for over 15 years. Its efficacy and safety have been well characterized through randomized trials, observational studies, and postmarketing surveillance.

Compared with deferoxamine and deferasirox, deferiprone appears to be equivalently effective at removing iron from the blood (serum ferritin) and liver (Ferriprox Product Monograph). However, it appears to have a preferential effect on two systems that can have a major impact on patients' lives: it is more effective than either deferoxamine or deferasirox for removing cardiac iron, and more effective than deferoxamine for clearing iron from endocrine organs.

<u>Improvements in cardiac iron, function, and mortality</u>

In the era when deferoxamine was the only chelation option, the primary cause of death in thalassemia major (50-70%) was cardiomyopathy and heart failure resulting from iron overload in the myocardium (Borgna-Pignatti Haematologica 2004, Modell JCMR 2008). This often occurred at a strikingly young age, with 15% to 50% of patients dying by the age of 35 years (Modell Lancet 2000).

In randomized clinical trials, deferiprone has been shown to be superior to deferoxamine for reducing the iron load in the heart (measured by the cardiac MRI parameter T2*) and in improving cardiac function as measured by left ventricular ejection function (LVEF) (Pennell Blood 2006). These improvements in iron levels and function appear to translate into survival benefits as well; a key observational study showed that switching from deferoxamine to deferiprone essentially eliminated cardiac events and deaths (Borgna-Pignatti Blood 2006), while a longitudinal registry study in the United Kingdom showed a dramatic 71% drop in deaths related to iron overload starting in the year 2000, when deferiprone became available along with MRI T2* as a method for identifying patients at high cardiac risk (Modell JCMR 2008). Due to these and other findings, the recent consensus guidelines of the

American Heart Association recommend deferiprone as the chelator of choice for patients at high cardiac risk (Pennell Circulation 2013). Although no studies have yet examined the impact of these cardiac benefits on years of life gained or improved quality of life, it stands to reason that improving heart function and reducing the risk of premature death are goals that will be meaningful to patients and their families.

Improvements in endocrine function

Although the main clinical endpoints considered in most thalassemia trials are serum ferritin, liver iron, and cardiac iron, iron overload can also affect endocrine organs such as the thyroid, gonads, and pancreas. The resulting complications of hypothyroidism, fertility issues, and diabetes can have a huge and often underappreciated impact on patients' activities and quality of life. In one longitudinal observational study, intensive combined treatment with deferiprone and deferoxamine was used in an attempt to normalize the body iron stores of patients with iron-related endocrine complications. Once iron levels had been normalized by the combined chelation, patients experienced dramatic improvements in endocrine function, notably:

- 44% of patients with previously impaired glucose metabolism saw it normalize
- 10 of 18 patients previously requiring thyroid hormone therapy were able to discontinue; 4 reduced their dose
- 7 of 14 previously hypogonadal males were able to stop their testosterone treatment
- 6 of 19 previously hypogonadal females were able to conceive

While no formal quality of life instruments were used to pinpoint the impact of these changes, the patients doubtless had improvements in their lives thanks to the decrease in comorbid conditions (and required medications) along with the ability to become parents when previously they had been unable (Farmaki BJH 2010).

Quality of life impact of oral chelators

Few studies have specifically addressed the quality of life dimensions of the different chelator options in a head-to-head manner, but the timing of their introduction to the market provides the opportunity for some indirect analyses. In Europe, deferiprone became available around 1999/2000, and deferasirox a few years later. As such, a quality of life analysis from Italy that looks at changes in the period from 2001 to 2009 reflects the availability of both oral agents compared to the previous deferoxamine-only era. The study found that compared to scores in 2001, patients in 2009 reported significant improvements in all scales of the SF-36, in particular the components relating to mental health. While the sample size was too small to discern the specific effects of particular oral chelating agents, the authors speculated that the greater ease of use of these medications, along with the reductions in cardiac mortality that occurred during that time period, could have helped improve patients' hopes for the future, their satisfaction with treatment, and their overall psychological well-being (Gollo Patient Prefer Adherence 2013). These findings are also supported by a small prospective analysis that found higher treatment adherence, physical and mental well-being, and self-esteem in the groups treated with a regimen that included an oral chelator (deferasirox alone or deferiprone-deferoxamine combination) compared with deferoxamine monotherapy (Goulas ISRN Hematology 2012).

Summary

Thalassemia is a rare disease, and as such the clinical trial record has some significant limitations in terms of head-to-head trials and analyses of "softer" endpoints such as quality of life. Likewise, few qualitative studies are available to speak specifically to the experience of patients and families living with thalassemia and its treatment. We believe that the clinical benefits of deferiprone will address

unmet needs in the Canadian chelation landscape and translate into an improved experience for patients with thalassemia and their families and caregivers. In particular, the improvements in cardiac morbidity/mortality and endocrine function have the potential to extend and transform the lives of patients suffering from iron-related complications, and the greater ease of compliance with an oral versus parenteral regimen should also bring significant relief to patients and their families.

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