Common Drug Review

Pharmacoeconomic Review Report

March 2016

Drug	deferiprone (Ferriprox)
Indication	The treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Listing request	As per indication.
Dosage form(s)	1000 mg tablets and 100 mg/mL oral solution
NOC date	February 13, 2015
Manufacturer	ApoPharma Inc.

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

TABLE OF CONTENTS

ABBREVIATIONS ii
EXECUTIVE SUMMARY v
INFORMATION ON THE PHARMACOECONOMIC SUBMISSION 1
1. Summary of the Manufacturer's Pharmacoeconomic Submission 1
2. Manufacturer's Base Case 2
3. Summary of Manufacturer's Sensitivity Analyses 2
4. Limitations of Manufacturer's Submission 2
5. CADTH Common Drug Review Reanalyses 3
6. Issues for Consideration 3
7. Patient Input 4
8. Conclusions 4
APPENDIX 1: COST COMPARISON 6
APPENDIX 2: SUMMARY OF KEY OUTCOMES 7
APPENDIX 3: ADDITIONAL INFORMATION 8
APPENDIX 4: REVIEWER WORKSHEETS 9
REFERENCES 23

Tables

Table 1: Summary of the Manufacturer's Economic Submission iii
Table 2: CADTH Common Drug Review Cost Comparison Table for Deferiprone for the Treatment of Iron Overload Due to Thalassemia Syndromes 6
Table 3: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Deferiprone Relative to Deferasirox Based on the Manufacturer's Submission? 7
Table 4: Submission Quality 8
Table 5: Authors' Information 8
Table 6: Data Sources 10
Table 7: Manufacturer's Key Assumptions 12
Table 8: Manufacturer's Base-Case Results for Deferiprone versus Deferasirox 15
Table 9: Manufacturer's Scenario Analysis Results for Deferiprone versus Deferasirox 16
Table 10: Manufacturer's Two-Way Sensitivity Analysis Assessing Dose Ranges for Deferiprone and Deferasirox 17
Table 11: Summary of CADTH Common Drug Review Reanalyses and Scenario Analyses (Deferiprone versus Deferasirox) 18
Table 12: Summary of CDR Reanalyses (Deferiprone versus Deferoxamine) 21

Figures

Figure 1: Manufacturer's Model Structure 9
Figure 2: Tornado Diagram Presenting Results of Manufacturer's Univariate Sensitivity Analyses 16

ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CEA	cost-effectiveness analysis
DFO	deferoxamine
DFP	deferiprone
DFX	deferasirox
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
TFC	Thalassemia Foundation of Canada
WTP	willingness-to-pay

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Deferiprone (Ferriprox) 1,000 mg tablet and 100 mg/mL oral solution
Study Question	"From the perspective of publicly funded health care payers in Canada, what is the relative cost-effectiveness of (deferiprone) compared with (deferasirox) in adults and children (regardless of treatment history or disease status) with transfusion-dependent thalassemia syndromes receiving iron chelation therapy for chronic iron overload?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate
Treatment	Deferiprone (Ferriprox), dosed at 25 mg/kg to 33 mg/kg body weight orally, three times per day (total daily dose = 75 mg/kg to 100 mg/kg)
Outcome	Quality-adjusted life year
Comparator	Deferasirox (Exjade)
Perspective	Publicly funded health care payers
Time Horizon	5 years
Results for Base Case	Deferiprone is more effective and less costly than (i.e., dominates) deferasirox
Key Limitations and CDR Estimates	CDR identified several key limitations with the manufacturer's economic submission. The main limitation was that not all relevant comparators to deferiprone were considered: deferoxamine in combination with deferiprone should have been assessed as a comparator. However, it was not possible for CDR to assess this comparison due to the lack of appropriate evidence comparing both treatment options for the outcomes of interest. CDR also identified the following main limitations from the submitted comparison of deferiprone versus deferasirox: • There were no data available to assess the comparative efficacy of deferiprone and deferasirox; thus, the manufacturer assumed that data from another treatment, deferoxamine, could be used to populate the deferasirox group of the model: comparative data of deferiprone versus deferoxamine. To test this assumption, CDR assumed no difference between deferiprone and deferasirox in terms of mortality and cardiac morbidity. This resulted in deferiprone being more effective and less costly than deferasirox, due to the greater cost of deferasirox at the doses used (deferiprone 75 mg/kg/day; deferasirox 30 mg/kg/day) and to the AE profiles applied for compared interventions. However, when AE rates were revised in the model, the small QALY benefit associated with deferiprone compared with deferasirox was lost. • Relative dosing of deferiprone and deferasirox differed based on patients' iron burdens and product monograph dose ranges. Reanalyses assessing the comparative doses of deferiprone and deferasirox based on feedback from the CDR clinical expert (deferiprone 75 mg/kg/day vs. deferasirox 30 mg/kg/day; deferiprone 100 mg/kg/day vs. deferasirox 40 mg/kg/day) found that deferiprone remains associated with fewer costs and more QALYs (i.e., dominant). The model is highly sensitive to comparative dosing regimens, which is a main driver of the model conclusion; altering the dose comparison unfavourably for deferiprone changes the direction of the results (ICUR > $500,000 for deferiprone versus deferasirox).

	• At the recommended dose of 25 mg/kg to 33 mg/kg three times a day (for a total daily dose of 75 mg/kg to 100 mg/kg 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, $55,747 for a daily dose of 30 mg/kg, and $74,329 for a daily dose of 40 mg/kg. • The potential combination use of deferiprone and deferoxamine would be associated with a non-negligible cost implication.

AE = adverse event; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; vs. = versus.

EXECUTIVE SUMMARY

Background

Deferiprone (Ferriprox) is an orally active iron chelating drug indicated for "the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate."[1] Deferiprone (DFP) is available as 500 mg tablets, 1,000 mg tablets, and 100 mg/mL oral solution.[1] The manufacturer is requesting reimbursement of the 1,000 mg tablet and the 100 mg/mL oral solution only, indicating that the 500 mg tablet will not be marketed in Canada. The recommended dose of DFP as listed in the Health Canada Product Monograph is 25 mg/kg to 33 mg/kg body weight orally three times a day, for a total daily dose of 75 mg/kg to 100 mg/kg body weight.[1]

The manufacturer-submitted prices are $30.36 per 1,000 mg tablet and $3.04 per 100 mg/mL oral solution, which are the currently marketed prices. Assuming an average body weight of 60 kg, the annual per-patient cost will range from $49,866 to $66,488 depending on the dose. The manufacturer is requesting listing as per the Health Canada indication.[1]

CADTH Common Drug Review (CDR) has previously reviewed deferasirox (DFX) for the management of chronic iron overload in patients with transfusion-dependent anemias. The former Canadian Expert Drug Advisory Committee (CEDAC) (now the Canadian Drug Expert Committee [CDEC]) recommended that DFX be listed for patients who require iron chelation, but in whom deferoxamine (DFO) is contraindicated.

The manufacturer submitted a cost-utility analysis[2] to establish the relative cost-effectiveness of DFP compared with DFX 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 by Bentley et al.,[3] which compared DFP alone with DFX alone, DFO alone, and DFP in combination with DFO (DFP-DFO) in the same population from the UK National Health Service perspective. The manufacturer used this model as a basis to capture differences in mortality, morbidity, quality of life (QoL), and resource use over a five-year time horizon (with annual cycles) from the perspective of publicly funded health care payers in Canada. Clinical efficacy inputs for the manufacturer's model were identified through the systematic review outlined in the article by Bentley et al.[3] The manufacturer indicated no new evidence had been published since the publication, and used the data from observational studies from the published review and model by Bentley et al.[3] Clinical efficacy parameters were taken from studies comparing DFP and DFO for which comparative efficacy data were available, as opposed to DFP versus DFX; the manufacturer assumed the efficacy of DFO could be applied to DFX. Data on adverse events (AEs) were sourced from the product monographs of DFP and DFX.[4,5] Utility and disutility values were sourced from published literature. Drug acquisition costs for each treatment were obtained from the Ontario Ministry of Health and Long-Term Care and from ApoPharma data on file. Costs for AEs were derived from UK data sources and converted to Canadian values. Monitoring costs were obtained from the Ontario Schedule of Benefits.[6,7]

The manufacturer reported that DFP was less costly and more effective than DFX.[2]

Summary of Identified Limitations and Key Results

CDR identified several limitations with the manufacturer's pharmacoeconomic submission, the main one being that the manufacturer did not consider all appropriate comparators: DFP-DFO was not assessed by

the manufacturer. DFX is not listed in all provinces; therefore, it is not the appropriate comparator in all jurisdictions. The CDR clinical expert noted that DFP could be added on to DFO.

Other key limitations identified by CDR from the submitted comparison of DFP versus DFX included:

- The data used to populate the efficacy input parameters in the model were associated with uncertainty; specifically, the absence of comparative data relating to the efficacy of DFP versus DFX led the manufacturer to assume that efficacy data for DFO could be used as a proxy for DFX.
- The manufacturer's analysis did not consider a broader range of dosing regimens which may be valid based on product monographs for DFP and DFX and CDR clinical expert input.
- The rates of AEs used and the generalizability of the UK costs associated with them were noted by CDR as being associated with some uncertainty.
- Monitoring costs may have been overestimated for DFX and DFP.

Based on CDR reanalyses of the previously mentioned limitations for DFP monotherapy versus DFX monotherapy, when varied independently, only treatment dose may alter the direction of the results in comparison with the manufacturer's base case, where DFP is associated with more quality-adjusted life-years (QALYs) and fewer costs (i.e., DFP dominates DFX). In a scenario applying equal mortality and cardiac morbidity, and varying drug costs in accordance with the comparative doses recommended by the CDR clinical expert (patients with lower iron burden: DFP monotherapy 75 mg/kg/day versus DFX monotherapy 30 mg/kg/day; patients with higher iron burden: DFP monotherapy 100 mg/kg/day versus DFX monotherapy 40 mg/kg/day), the results still showed that DFP monotherapy is associated with more QALYs and fewer costs. However, when adding in revised AE rates, the minimal QALY benefit associated with DFP compared with DFX monotherapy no longer exists.

It was not possible for CDR to assess the comparison of DFP monotherapy with combined DFO and DFP due to the lack of appropriate evidence comparing both treatments options for the outcomes of interest. Of note, an exploratory analysis was developed by CDR comparing DFP with DFO alone (APPENDIX 4).

Conclusions

CDR identified limitations in the assessment of the cost-effectiveness of DFP in patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate, compared by the manufacturer with DFX; the limitations mainly result from the weakness of the clinical evidence available for this cost-effectiveness comparison and the drug dosages assessed by the manufacturer. Additionally, the manufacturer did not assess the comparison of DFP versus DFP-DFO.

There is high uncertainty associated with the comparative clinical effects and harms of DFP monotherapy compared with DFX monotherapy; the superiority of one versus the other has not been proven. Based on the comparative doses recommended by the CDR clinical expert, the reanalyses undertaken by CDR using the manufacturer's model concluded that DFP monotherapy may be less costly than DFX monotherapy. However, altering the dose comparison unfavourably for DFP changes the direction of the results in favour of DFX.

At the recommended dose of 75 mg/kg to 100 mg/kg per day, the annual cost of DFP ranges from $49,866 to $66,488 (assuming a 60 kg patient); the annual cost of DFX is $37,165 for a daily dose of

20 mg/kg, $55,747 for a daily dose of 30 mg/kg, and $74,329 for a daily dose of 40 mg/kg (assuming a 60 kg patient).

It was not possible for CDR to assess the comparison of DFP with combined DFP and DFO. However, if DFP is to be used as dual therapy, it would be associated with a non-negligible cost implication.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) comparing deferiprone (DFP) with deferasirox (DFX) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The submitted model was a three-state Markov model with annual cycles and was based on a model published in *Pharmacoeconomics* by Bentley et al.[3] The Bentley et al. publication presented an analysis comparing DFP alone with DFX alone, deferoxamine (DFO) alone, and DFO combined with DFP in adults and children with transfusion-dependent beta thalassaemia receiving iron chelation therapy for chronic iron overload from the perspective of the UK National Health Service. Patients could be in one of the following health states: alive with no cardiac disease; alive with cardiac disease; or dead. The model is similar to others presented in the published literature.[9] The risk of cardiac morbidity and cardiac mortality drive the analysis, and are assumed to be constant over time and independent of one another. For each treatment group, the risk of death is equal in both "alive" health states. A five-year time frame is employed, reflecting the duration of cardiac morbidity and mortality studies utilized for the analysis. The cycle length is one year.[2]

In the model, all patients are assumed to be in the "alive without cardiac disease" group in year 1. The model then incorporates the differential risks of transitioning to "alive with cardiac disease" and "death" states in year 2 through year 5. A half-cycle correction was not applied. No randomized studies or meta-analyses have been published that compare DFP with the primary comparator in the manufacturer's analysis, DFX. Thus, efficacy data for DFO were used as a proxy for DFX, based on studies comparing DFP and DFO. Cardiac morbidity transition probabilities are informed by data from a retrospective review by Piga et al.[10] that focused on a comparison of DFP with DFO in patients with thalassemia major; the cardiac mortality transition probabilities are informed by data from a report based on a prospective multi-centre randomized clinical trial by Maggio et al.[11] that focused on the same individual comparators and their use in combination in patients with thalassemia major. Natural history data are mentioned in the report, but not incorporated in the model, due to the short nature of the model and the assumption that no one discontinues treatment with either DFP or DFX.[2]

Health-state utility values were based on a published economic evaluation of DFX in the UK,[12] while disutility values due to adverse events (AEs) were sourced from a variety of published articles[13-15] through the Tufts Cost-Effectiveness Analysis (CEA) Registry.[16] AE rates were stated to be based on DFP and DFX product monographs (non-Canadian),[4,5] published literature,[17] and assumptions. Drug costs were sourced from the Ontario Exceptional Access Formulary[18] for DFX and from ApoPharma data on file for DFP.[2] Monitoring costs were sourced from the Ontario Schedule of Benefits for Laboratory Services[7] and the Ontario Schedule of Benefits for Physician Services.[6] AE costs were derived from UK data sources and converted to Canadian dollars.

The manufacturer undertook five scenario analyses, excluding cardiac mortality and cardiac morbidity independently, excluding and doubling AE costs over a five-year time horizon, and assuming treatment did not affect cardiac morbidity or mortality, assessed over a one-year time horizon. The manufacturer assessed uncertainty surrounding the model inputs through a series of one-way, two-way, and probabilistic sensitivity analyses.

The manufacturer reported that the model used has previously been peer reviewed and published in *Pharmacoeconomics*.[3] Updated inputs were validated by a Canadian clinician. Numerical validation of the model was performed by health economists from Abacus International.[2]

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case analysis reported that DFP was more effective and less costly than DFX, accruing an extra 0.096 quality-adjusted life-years (QALYs) (3.81 QALYs for DFP) at a lower cost ($230,000 versus $253,000) over the five-year time horizon (Table 8).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer reported that in each scenario analysis, DFP dominated DFX (Table 9). However, the univariate sensitivity analysis indicated that the model was particularly sensitive to the daily dose of DFX, the daily dose of DFP, and the annual use of DFX (Figure 2). The manufacturer's two-way sensitivity analysis testing different dose ranges for DFP and DFX indicated that the acquisition cost of DFP may not be less than DFX, as shown in the base case (range [DFP minus DFX]: –$38,570 to $135,009) (Table 10).

The manufacturer's probabilistic sensitivity analysis concluded that at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained, the probability that DFP is cost-effective is 96.86%; this increases to 98.8% at a WTP threshold of $100,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CADTH Common Drug Review (CDR) identified the following primary limitation with the manufacturer's pharmacoeconomic submission:[2]

- **The analysis did not consider all relevant comparators.** Feedback from the CDR clinical expert and information from the clinical practice guidelines indicated that DFX is not the only appropriate comparator. DFO in combination with DFP (DFO-DFP) is also an appropriate comparator.

CDR identified the following key limitations with regards to the data used to inform the manufacturer's pharmacoeconomic submission:

- **There is substantial uncertainty regarding the comparative efficacy of DFP and DFX and the data used to populate DFX in the model.** The manufacturer reported that no head-to-head comparison of DFP and DFX was available; thus, data from two observational studies comparing DFP with DFO were used, with the assumption that it was appropriate to use DFO data as a proxy for DFX. No mention was made of the potential for a mixed treatment comparison. CDR clinical reviewers appraised the evidence that the manufacturer provided to justify this assumption, and concluded that while the available data indicate that DFX and DFO appear similar, there is uncertainty regarding the actual comparative effectiveness of DFX versus DFO. To populate the analysis, the manufacturer used data from two studies — identified out of a total of 20 — that reported their outcomes of interest (cardiac morbidity and cardiac mortality) for DFP versus DFO alone, and with add-on DFP in patients with thalassemia major. The publications used are associated with uncertainty, confounding, and bias due to the collection of data (observational study) or the way the data were reported. The CDR Clinical Review identified conflicting clinical evidence regarding the comparison of DFP with DFO.

- **Relative dosing of DFP and DFX may favour DFO.** The model used the lower-level dosing for DFP and the upper level for DFX, which may have biased the results in favour of DFP. The CDR clinical expert noted that dosing of DFP and DFX will vary within their dose ranges depending upon the patient's characteristics (i.e., level of iron burden). Based on feedback from the CDR clinical expert, CDR undertook analyses comparing DFP monotherapy 75 mg/kg/day with DFX monotherapy 30 mg/kg/day (for patients with lower iron burden), and comparing DFP monotherapy 100 mg/kg/day with DFX monotherapy 40 mg/kg/day (for patients with higher iron burden). Given the ranges provided for DFX in the product monographs and guidelines, CDR also tested DFP monotherapy 100 mg/kg/day compared with DFX monotherapy 30 mg/kg/day and DFP monotherapy 75 mg/kg/day compared with DFX monotherapy 20 mg/kg/day in sensitivity analyses.
- **Rate and costs of AEs.** The manufacturer used dated data for AEs, and CDR was not able to identify some of the rates presented by the manufacturer for AEs. The AE costs were sourced from the UK and may not be applicable in Canada. CDR undertook some revised estimates of AEs and costs.
- **Monitoring costs may have been overestimated for DFX.** The CDR clinical expert indicated that the manufacturer may have overestimated the resource intensity of monitoring for both treatments, but for DFX in particular. CDR tested revised estimates.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook reanalyses for DFP compared with DFX as per the manufacturer's base-case analysis. Lack of data prevented the comparison of DFP versus DFP-DFO. CDR undertook an exploratory analysis for DFP compared with DFO (APPENDIX 4).

CDR undertook analyses of varying treatment doses, monitoring costs, AE rates and costs, and efficacy assumptions. The results of the CDR analyses of DFP compared with DFX indicated a wide range of outcomes, with drivers being the comparative drug dosages and relative efficacy and safety. When the relative drug dosages were varied unfavourably for DFP from the base-case recommended dosages (DFP monotherapy 75 mg/kg/day versus DFX monotherapy 30 mg/kg/day; DFP monotherapy 100 mg/kg/day versus DFX monotherapy 40 mg/kg/day), results changed to an incremental cost-utility ratio (ICUR) > $500,000 per QALY for DFP monotherapy versus DFX monotherapy. At the comparable doses recommended by the CDR clinical expert, when equal mortality and cardiac morbidity are assumed and no other revisions are made, DFP was associated with more QALYs and fewer costs than DFX. Using the base-case dosages, assuming equal mortality and cardiac morbidity, revising non-drug costs, and varying AEs input unfavourably for DFP resulted in DFP being associated with fewer QALYs and costs than DFX, but with ICURs > $30 million per QALY for DFX versus DFP.

6. ISSUES FOR CONSIDERATION

- The CDR clinical expert indicated there is the potential for patients to receive DFP as a first-line treatment, outside indication. The use of DFP as a first-line treatment may be expected to be associated with a higher cost-effectiveness ratio and increased budget impact.
- The CDR clinical expert indicated that treatment switching and addition for combinations is common between treatments; the addition of one drug to another (in comparison with switching to another drug) has major cost implications. Appropriate guidance is needed for the optimal usage of these drugs for best use of public resources.

- The CDR clinical expert indicated that DFP, like other chelation therapies, will not affect the number of blood transfusions required by patients.
- Although DFO is reported to be much cheaper, there are substantial drawbacks to its use, such as administration requirements due to short half-life, which affects adherence. DFO in practice is generally used in combination with other iron chelating drugs.

7. PATIENT INPUT

Patient input was received from the Thalassemia Foundation of Canada (TFC). Although TFC receives funding from ApoPharma and Novartis, no conflicts were declared. TFC gathered information for the input from a variety of sources, including medical literature (PubMed), a 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.

TFC noted that if left untreated, iron overload is usually fatal due to iron buildup in the myocardium and consequent heart dysfunction. Patients and caregivers indicate that the condition disrupts their ability to work or attend school, as well as their physical and social interactions, with substantial amounts of time and effort spent on treatment. Patients also reported that the condition affects their attitude toward having children, thinking that it may not be appropriate for them to have children given their own personal burden, but also considering the risk of passing on the genetic syndrome.

TFC reported that published information highlights the demanding administration requirements of DFO (half-day infusion, five to seven days a week); side effects may add to patients' treatment burden. DFP and DFX are oral tablets noted to be effective and improve patients' quality of life (QoL) while reducing treatment burden. It was considered in the CDR analysis comparing DFP with DFO, a reduction in patient QoL associated with the parenteral use of DFO. Furthermore, side effects and a dislike of the taste/texture of DFX were noted as important barriers to treatment adherence; this was not directly considered in the cost-effectiveness assessment.

TFC suggested that data support the effectiveness of DFP, noting its potential benefits over other treatments (DFO and DFX) in removing cardiac iron, which could translate into reduced cardiac mortality and morbidity — a major feature considered by the model. TFC also noted that an additional oral chelation option could improve adherence and QoL beyond current options.

8. CONCLUSIONS

CDR identified limitations in the assessment of the cost-effectiveness of DFP compared with DFX in patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The limitations mainly result from the weakness of the clinical evidence available for this cost-effectiveness comparison and the drug dosages assessed by the manufacturer. Additionally, the manufacturer did not assess the comparison of DFP with combined DFP and DFO.

There is high uncertainty associated with the comparative clinical effects and harms of DFP monotherapy compared with DFX monotherapy; the superiority of one versus the other has not been proven. Based on the comparative doses recommended by the CDR clinical expert, the reanalyses undertaken by CDR using the manufacturer's model concluded that DFP monotherapy may be less costly

than DFX monotherapy. However, altering the dose comparison unfavourably for DFP changes the direction of the results in favour of DFX.

At the recommended dose of 75 mg/kg to 100 mg/kg per day, the annual cost of DFP ranges from $49,866 to $66,488 (for a 60 kg patient); the annual cost of DFX is $37,165 for a daily dose of 20 mg/kg, $55,747 for a daily dose of 30 mg/kg, and $74,329 for a daily dose of 40 mg/kg (for a 60 kg patient).

It was not possible for CDR to assess the comparison of DFP alone versus DFP-DFO. However, if DFP is to be used as dual therapy, it would be associated with a non-negligible cost implication.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 2 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 2: CADTH COMMON DRUG REVIEW COST COMPARISON TABLE FOR DEFERIPRONE FOR THE TREATMENT OF IRON OVERLOAD DUE TO THALASSEMIA SYNDROMES

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[a]	Annual Drug Cost ($)[b]
Deferiprone (Ferriprox)	**1,000 mg 100 mg/mL**	**Tablet Oral Solution**	**30.3600[c] 3.0360[c]**	**25 mg/kg to 33 mg/kg per dose, three times daily (total daily dose: 75 mg/kg to 100 mg/kg)**	**49,866 to 66,488**
Deferasirox (Exjade)	125 mg 250 mg 500 mg	Tablet for suspension	10.6064 21.2125 42.4253	10 mg/kg to 30 mg/kg once daily (though doses up to 40 mg/kg may be considered)	18,582 (10 mg) 37,165 (20 mg) 55,747 (30 mg) 74,329 (40 mg)
Deferoxamine[d] (Desferal)	500 mg/vial 2.0 g/vial	Lyophilized powder in vials for IV, SC, or IM infusion[e]	14.5790[f] 57.5300[f]	**SC/IV:** 1 to 4 g (20 mg/kg to 60 mg/kg) over a period of approximately 12 hours **IM:** 0.5 g to 1 g daily (1 to 2 injections) Dosing is 4 to 7 times per week.	20,998 to 31,641[g]
Deferoxamine[d] (generics)	500 mg/vial 2.0 g/vial	Lyophilized powder in vials for IV, SC, or IM infusion[e]	5.0763[f] 20.4027[f]	**SC/IV:** 1 g to 4 g (20 mg/kg to 60 mg/kg) over a period of approximately 12 hours **IM:** 0.5 g to 1 g daily (1 to 2 injections) Dosing is 4 to 7 times per week.	7,447 to 11,153[g]

IM = intramuscular; IV = intravenous; SC = subcutaneous.
[a] As per product monographs.[1,20-22]
[b] Based on a 60 kg patient (average patient weight in the economic evaluation).
[c] Manufacturer-submitted price.
[d] Also listed as desferrioxamine.
[e] Single-use vial.
[f] Alberta BlueCross Drug Formulary (October 2015). Unit price (per vial).
[g] The clinical expert indicated that the dose range for DFO was 35 mg/kg to 50 mg/kg, so that range is what is listed in the Annual Drug Cost column (2.1 g to 3 g per administration). Dosing is dependent upon iron load. Dosing was assumed to be seven days per week.
Note: Drug prices are taken from the Ontario Formulary Exceptional Access Program (October 2015) unless otherwise indicated, and do not include prescription fees, costs of dose preparation, or administration fees.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 3: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DEFERIPRONE RELATIVE TO DEFERASIROX BASED ON THE MANUFACTURER'S SUBMISSION?

Deferiprone versus Deferasirox	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	DFP dominates DFX					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; DFP = deferiprone; DFX = deferasirox; NA = not applicable.
Note: As noted in the table title, CDR reviewers have based these grades on the manufacturer's base-case submission to CDR. CDR noted substantial uncertainty with regards to several inputs in the manufacturer's analysis, which could alter the listed assessments.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 4: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?			X
Comments	The broad indications for DFP, DFX, and DFO approved by Health Canada allow for a broader scope of use than was included in the economic analysis. Use of DFP in combination with DFO, or a comparison of DFP with DFO individually should have been undertaken as part of the primary economic analysis.		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

TABLE 5: AUTHORS' INFORMATION

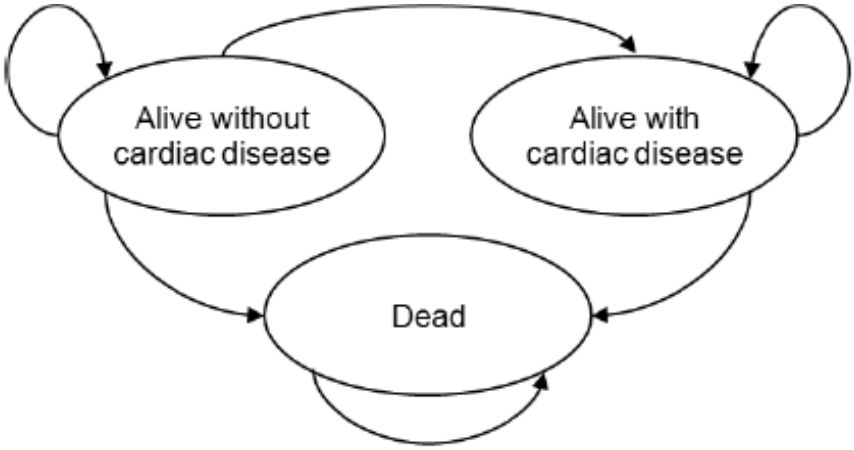
Authors of the pharmacoeconomic evaluation submitted to			
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis (CUA) comparing deferiprone (DFP) with deferasirox (DFX) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The analysis presented a three health-state Markov model with annual cycles; patients can be alive with no cardiac disease; alive with cardiac disease; or dead (Figure 1). The Markov model was based on one published in *Pharmacoeconomics*.[3] The published model was used to assess the cost-effectiveness of DFP alone compared with DFX alone, deferoxamine (DFO) alone, and DFP in combination with DFO (DFP-DFO) in adults and children with transfusion-dependent beta thalassaemia receiving iron chelation therapy for chronic iron overload from the perspective of the UK National Health Service. The model structure is consistent with other economic evaluations modelling iron chelation therapies.[9]

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



Source: Manufacturer's pharmacoeconomic submission.[2]

The manufacturer indicated that no randomized controlled trials (RCTs) or network meta-analyses have been identified comparing DFP with DFX. No RCTs provide direct evidence of the effect of these treatments on cardiac morbidity and mortality. Thus, to determine effect on cardiac morbidity, the manufacturer indicated that cardiac T2* MRI (magnetic resonance imaging) data were used to demonstrate that the relative risk of heart failure or arrhythmia increases linearly as T2* times decrease from 20 ms. The manufacturer noted that DFX had an effect similar to DFO on this outcome in observational studies;[23,24] thus, in the absence of head-to-head data comparing DFP and DFX, it was decided that cardiac mortality and morbidity outcomes from observational studies of DFO (studies comparing DFO with DFP) could be used as a proxy for cardiac mortality and morbidity outcomes for DFX.

A five-year time frame was employed, reflecting the duration of cardiac morbidity and mortality in the studies used in the analysis. The cycle length was one year. Cardiac morbidity and mortality were assumed to be constant over time and independent of one another. The manufacturer indicated that this assumption was made as the data for cardiac morbidity and cardiac mortality applied in the model

were from different studies; thus, no linkages could be identified. The manufacturer indicated the risk of death is equal in both "alive" health states.[2]

In year 1, all patients were assumed to be in the "alive without cardiac disease" health state for the entire year. The model then incorporated differential risks of transitioning to "alive with cardiac disease" and "death" states in year 2 through year 5. The transitions occurred at the start of the year. A half-cycle correction was not applied.

The manufacturer reported that clinical inputs for the model were based on a systematic review of the literature. A total of 20 publications (11 RCTs and nine non-RCTs) were identified as potentially relevant to inform the model inputs. In the model, cardiac morbidity transition probabilities were informed by data from a retrospective review by Piga et al.[10] comparing DFP and DFO; cardiac mortality transition probabilities were informed from a report of a prospective multi-centre RCT by Maggio et al.[11] that compared DFP alone with DFO alone, as well as their use in combination and sequentially. Natural history data are mentioned in the manufacturer's pharmacoeconomic report, but are not incorporated in the model, presumably due to the short-term nature of the model and the manufacturer's assumption that no patients, while alive, discontinued treatment with either DFP or DFX.[2] Only adverse events (AEs) mentioned as areas of concern within the product monograph were included in the manufacturer's model. Though no quantitative data were available for thalassemia patients with transfusional iron overload, the manufacturer assumed that DFX was not associated with excess mortality due to AEs.

Utility values were sourced as per Bentley et al.[3] The base health-state utility value was sourced from a published economic evaluation of DFX compared with DFO in the UK,[12] which gathered values from a time trade-off exercise administered to 120 members of the general population. Utility associated with cardiac morbidity was based on average utility values listed on the Tufts Cost-Effectiveness Analysis (CEA) Registry.[16] Disutility values due to AEs were sourced from a variety of published articles[13-15] through the Tufts CEA Registry.[16] AE rates were based on DFP and DFX product monographs from the US and Europe,[4,5] published literature,[17] and assumptions.

Drug costs were sourced from the Ontario Exceptional Access Formulary[18] for DFX and ApoPharma data on file for DFP.[2] The frequency and resource use associated with monitoring were based on product monographs, American Heart Association guidelines, Guidelines for the Clinical Care of Patients with Thalassemia in Canada, and expert opinion. Monitoring costs were sourced from the Ontario Schedule of Benefits for Laboratory Services[7] and Ontario Schedule of Benefits for Physician Services.[6] AE costs were derived from UK data sources and converted to Canadian dollars.

TABLE 6: DATA SOURCES

Data Input	Description of Data Source	Comment*
Efficacy: Cardiac morbidity	The proportion of patients with cardiac disease was based on a retrospective analysis by Piga et al. 2006[10] assessing DFP vs. DFO.	Cardiac disease data for DFO from an observational study were used as a proxy for cardiac morbidity data for DFX, as there is no head-to-head RCT or NMA comparison of DFP and DFX.
Efficacy: Cardiac mortality	The proportion of patients with cardiac mortality was based on an open-label, multi-centre trial of DFP vs. DFO vs. DFP-DFO by Maggio et al. 2009.[11]	Cardiac mortality data for DFO from an observational study were used as a proxy for DFX (as mentioned). DFO had a higher mortality rate than DFP in the observational

Data Input	Description of Data Source	Comment*
		study; this contradicts earlier text from the manufacturer's submission regarding AEs, which indicated DFX was not associated with excess mortality. Data from Maggio et al. may be biased, as they do not appear to take into account the treatment to which patients who died were randomized for the trial (all were randomized to either DFP or DFP-DFO).
Natural history	Briefly reported that thalassemia is a chronic condition; thus, patients receiving regular transfusions will require lifelong iron chelation to remove excess iron.	In the model, all patients receive iron chelation therapy and no patients discontinue treatment.
AEs	Only AEs that were specifically mentioned as areas of concern within the product monographs[4,5] and were likely to affect health care costs and QoL were included in the model: • Agranulocytosis • Neutropenia • Hepatitis • Fanconi Syndrome	The CDR clinical expert indicated that arthralgia and increased ALT are important patient considerations, but would not be associated with substantial resource use or cost. The source used for the incidence of hepatitis[5] does not seem to reference the value used in the model.
Utilities	The manufacturer's model does not mention QoL data captured in the RCT (LA16-0102).[25]	LA16-0102 captured HRQoL scores through the RAND 36.[25] The RAND 36 contains the same questions as the Short Form 36 (SF-36), but is scored in a different way. Thus, the manufacturer could have derived utility values from the LA16-0102 trial.
Iron chelation therapy (base value)	Patients receiving iron chelation therapy were reported to have a utility of 0.840; this was estimated for oral DFX using the TTO method by Karnon et al.[12]	The TTO exercise was conducted in a general population sample in the UK, attempting to recreate results from an earlier Australian study.[19] The utility for patients receiving infusion was 0.66.
Cardiac morbidity	Assumed the same methodology as Bentley et al. 2013[3] when patients with cardiac morbidity were assumed to have the mildest form (NYHA class I). The manufacturer searched the Tufts CEA database and averaged a range of utility scores to calculate a value to populate the model (0.921) (sources not specified).	This utility value is higher than the baseline values for chelation therapies; thus, the manufacturer calculated and applied a proportional decrement to the utility value for chelation. If cardiac benefit is assumed for DFP, then the value used may be a conservative assumption. If a more severe form of cardiac disease was used (e.g., NYHA II), then the utility value would decrease (recent papers suggest a range from 0.78 to 0.855).
Adverse events	Utility scores for each AE were obtained from the published literature and proportional decrement applied. Duration of utility decrement for the AE was based on expert opinion from three specialists.	The CDR clinical expert indicated the durations presented were appropriate.

Data Input	Description of Data Source	Comment*
Resource use: frequency of monitoring	Information on tests and frequency of testing were based on product monographs from the US and Europe,[4,5] American Heart Association guidelines,[26] expert opinion, and Canadian Guidelines for the Clinical Care of Patients with Thalassemia.[27]	The CDR clinical expert indicated some minor changes in frequency of monitoring functions, as well as additional monitoring requirements for DFO.
Costs		
Drug	Cost of DFX was sourced from the Ontario Drug Benefit Exceptional Access Program.[18] Cost of DFP was based on ApoPharma data on file. Patient weight (60 kg) was based on Canadian clinical expert opinion and supported by US data (57 kg) – International Classification of Diseases 9th Revision code 282.44.[2] The manufacturer's stated daily dose was based on the midpoint of each product monograph.[4,5]	Appropriate drug cost sources. The patient weight was accepted by the CDR clinical expert as appropriate. The daily doses do not appear to have been midpoints of treatment ranges, but to have been presented in a way that best presents the results for DFP. The DFP dose range per Canadian product monograph[1] and LA16-0102[8] was 75 mg/kg to 100 mg/kg, though a dose of 75 mg/kg used; the DFX dose was reported to range from 10 mg/kg to 30 mg/kg,[20] though a dose of 30 mg/kg was used.
Administration	Oral treatments; no administration cost.	Appropriate.
Event: Cardiac morbidity	As noted earlier, cardiac morbidity was assumed to be the least severe NYHA class; thus, it would incur no costs.	
AEs	Manufacturer reported that Canadian costs were not available; thus, the UK costs reported in Bentley et al.[3] were used and converted to Canadian dollars through the PPP index. Costs for hepatitis were based on a separate UK study.[28]	AE costs from the UK are not applicable to the Canadian setting, particularly when there are Canadian costs available.
Monitoring	Test costs were obtained from the Ontario Schedule of Benefits for Laboratory Services.[7]	

AE = adverse event; ALT = alanine aminotransferase; CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; DFO = deferoxamine; DFP = deferiprone; DFX = deferasirox; HRQoL = health-related quality of life; NMA = network meta-analysis; NYHA = New York Heart Association; PPP = Purchasing Power Parity; QoL = quality of life; RAND 36 = 36-item Short Form Survey from the RAND Medical Outcomes Study; RCT = randomized controlled trial; TTO = time trade-off; vs. = versus.

TABLE 7: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The only relevant comparator is DFX.	The wording of the Health Canada–approved product monographs for DFP, DFO, and DFX does not indicate that they cannot be used sequentially or, for the first two, in combination (DFP-DFO). This was not taken into account in the submission to CDR (though it was presented in the publication upon which the model was based). The CDR clinical expert indicated that although DFO may be recommended as the first-line drug, in

Assumption	Comment
	clinical practice there is a move toward the use of oral drugs, given the treatment burden and AEs associated with DFO. The wording of the DFX indication as a treatment to be used "when current chelation therapy is inadequate" is very broad; there is substantial uncertainty as to what constitutes current chelation therapy. CDR suggests a primary comparison of DFP vs. DFP-DFO would also have been appropriate to include.
No patients discontinue or switch treatments.	The CDR clinical expert indicated that this assumption was not likely to be appropriate. A high proportion of patients stop or switch treatments for reasons related to harms, tolerability, or efficacy. The DFP product monograph indicates DFP should not be used in patients who have had agranulocytosis.
A 5-year time horizon is appropriate.	The manufacturer states in its document that all patients with beta thalassemia major receiving regular transfusions are at risk of iron overload; therefore, they require lifelong chelation therapy. CDR notes there is a lack of long-term follow-up data to assess effectiveness and safety over time.
The average weight of a beta thalassemia patient in Canada is conservatively estimated to be 60 kg.	Appropriate. The manufacturer provided data from the US that indicated an average weight of 57 kg, and the CDR clinical expert indicated that most patients seen currently in Canada are adults; therefore, the assumption is appropriate.
Patients with cardiac morbidity have the mildest form (NYHA class I).	This was the case for the assumption of utility data and cost information; however, it does not seem to have been used as an identifier in determining clinical information, as there was no delineation in the observational studies regarding severity of disease. If a cardiac morbidity benefit is accepted, this would be a conservative approach against DFP.
No randomized controlled studies or network meta-analyses were identified that directly compared DFP and DFX, or that provided direct evidence of ICT effects on cardiac morbidity and mortality. Cardiac T2* MRI data were reported to have been used as a proxy to justify the assumption that DFX had a similar effect on cardiac outcomes to DFO (based on a T2* score of less than 6 ms), based on data from observational studies.[23,24] Thus, the assumption was made that it was appropriate for DFO data to be used as a proxy for DFX (that is, that DFO and DFX are essentially equivalent).	The assumption that DFX is similar or equivalent to DFO may not be appropriate. The evidence that suggests comparative effectiveness is associated with uncertainty, given the issues with bias and confounding in observational studies and the lack of an appropriately conducted network meta-analyses or head-to-head RCT. This choice of data is highly questionable given the totality of the information available. When looking at this from a Canadian practice viewpoint, not all facilities have access to cardiac MRIs. However, the CDR clinical expert indicated that in practice, there is a difference between DFP and DFX regarding cardiac benefits that is not necessarily seen between DFX and DFO.
Mortality and morbidity (cardiac disease) risks are assumed to be constant over time and independent of one another. The independence is a simplifying assumption. Since the cardiac morbidity and mortality data are taken from two separate studies, it is not possible to directly link the cardiac mortality data to those patients with cardiac morbidity.	As the manufacturer indicated, given the nature of the data, it is appropriate that cardiac morbidity and cardiac mortality are considered independently; however, in practice, it is unknown whether this is the case. There is substantial uncertainty as to whether the risks would be constant over time.

Assumption	Comment
The use of DFO data as a proxy for DFX for both the cardiac morbidity and cardiac mortality parameters was appropriate based on cardiac T2* MRI data.	This is not an appropriate assumption. The cardiac T2* MRI data are essentially a proxy for cardiac morbidity; yet, given that the manufacturer has indicated there is no link between cardiac morbidity and cardiac mortality, the validity of this methodology is not justified.
The Maggio et al.[11] paper is appropriate to determine morbidity data for DFP and DFX (DFO).	The Maggio et al.[11] paper reports Kaplan–Meier survival curves for the four chelation treatments. However, it appears that these are based on the treatment patients were receiving just prior to death, as opposed to what treatment (if any) they were randomized to. Data reported in Table 2 of Maggio et al. appear to differ from information reported in the text of the paper.
The risk of death is equal in both "alive" health states.	May not be appropriate.
The use of utility values derived by Karnon et al.[12] is the most appropriate estimate.	As noted in Karnon et al.,[12] the authors attempted to replicate the results of an Australian study by Osborne et al.[19] The study by Osborne et al. included an "anchor state" where the mode of administration was unspecified (mean = 0.75; median = 0.80). The base utility value in the manufacturer's model (0.84)[12] is lower than other available estimates on the assumption of oral chelation (mean = 0.85; median = 0.93).[19] If the model included DFO, as CDR suggests, the base utility value might be closer to the manufacturer's estimate.
The dose of DFP is 75 mg/kg.	Although the average dose in the clinical trial and text from the Canadian Guidelines for the Clinical Care of Patients with Thalassemia appear to support this assumption,[27] the guidelines were published well before DFP was licensed for use in Canada. The CDR clinical expert indicated that with experience in clinical practice, the daily dose of DFP as monotherapy is likely to be at the maximum recommended dose of 100 mg/kg in patients with a higher iron burden. The use of a higher dose of DFP monotherapy is supported by text from the pivotal study LA16-0102: *Oral DFP was initiated at 75 mg/kg/day and increased to the target of 100 mg/kg/day*.[8]
The dose of DFX is 30 mg/kg.	The CDR clinical expert indicated that in practice, the average daily dose of DFX ranges from 20 mg/kg to 40 mg/kg as monotherapy depending upon the patient's iron burden; when used in combination with other ICTs, the daily dose may be reduced (range: 20 mg/kg to 30 mg/kg). The Canadian Guidelines for the Clinical Care of Patients with Thalassemia indicates a dose between 10 mg/kg and 30 mg/kg, suggesting a lower dose may be appropriate; however, the impact on effectiveness and safety appears to differ based on dose. The product monograph does indicate that in patients with beta thalassemia who are not adequately controlled with daily doses of 30 mg/kg, doses of up to 40 mg/kg may be considered. The CDR clinical expert indicated that the daily dose of DFO ranges between 35 mg/kg and 50 mg/kg, which is maintained when used in combination with other ICTs. No studies have been undertaken on dose equivalence.

Assumption	Comment
Treatment with ICT is not expected to affect the number of blood transfusions a patient receives.	Appropriate. CDR clinical expert indicated the impact of DFP on the proportion of patients requiring blood transfusions to be minimal.
It is appropriate that a half-cycle correction was not applied.	Considering the relatively long-term cycles of one year, the exclusion of a half-cycle correction is not likely to be appropriate.

CDR = CADTH Common Drug Review; DFO = deferoxamine; DFP = deferiprone; DFX = deferasirox; ICT = iron chelation therapy; MRI = magnetic resonance imaging; NYHA = New York Heart Association; RCT = randomized controlled trial; vs. = versus.

The manufacturer undertook three scenario analyses:

- Scenario 1 excludes the "alive with cardiac disease" health state, and only considers cardiac mortality over a five-year time horizon.
- Scenario 2 excludes the effect of cardiac mortality, and considers cardiac morbidity over a five-year time horizon.
- Scenario 3 assumes the chelation therapies do not affect cardiac morbidity or mortality; thus, it considers the costs and quality of life (QoL) attributable to administration- and treatment-related AEs over a one-year time horizon.

Two additional scenarios were undertaken where AEs were considered to have no cost (Scenario 4) or to be double the stated cost (Scenario 5).

The manufacturer assessed uncertainty surrounding the base-case model inputs through a series of one-way, two-way, and probabilistic sensitivity analyses on efficacy, AEs, monitoring, dosing, and cost parameters.

The manufacturer reported that the model used has previously been peer reviewed and published in *Pharmacoeconomics*.[3] Updated inputs were validated by a Canadian clinician. Numerical validation of the model was performed by health economists from Abacus International.[2]

Manufacturer's Results

The manufacturer's base-case analysis reported that DFP was more effective and less costly than DFX (Table 8).

TABLE 8: MANUFACTURER'S BASE-CASE RESULTS FOR DEFERIPRONE VERSUS DEFERASIROX

Parameters	Deferiprone	Deferasirox	Incremental change (DFP – DFX)
Drug costs	$226,690	$248,709	–$22,019
Monitoring costs	$2,980	$4,991	–$2,011
AE costs	$606	$33	$573
Total costs	**$230,275**	**$253,733**	**–$23,458**
QALYs	**3.813**	**3.717**	**0.096**
ICUR	**NA**	**NA**	**Dominant**

DFP = deferiprone; DFX = deferasirox; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[2]

Summary of the Manufacturer's Sensitivity Analyses

The manufacturer reported that in each of the scenario analyses, DFP dominated DFX (Table 9).

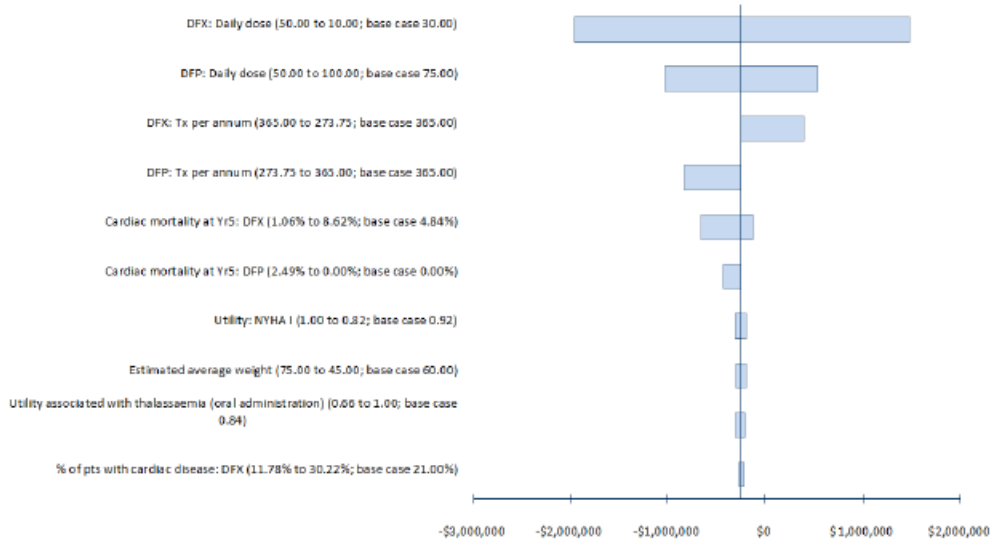
TABLE 9: MANUFACTURER'S SCENARIO ANALYSIS RESULTS FOR DEFERIPRONE VERSUS DEFERASIROX

Scenario Analysis	Incremental Cost (DFP – DFX)	Incremental QALYs (DFP – DFX)	ICUR
Scenario 1: No between-treatment difference for cardiac morbidity	–$23,458	0.076	**Dominant**
Scenario 2: No between-treatment difference for cardiac mortality	–$28,267	0.026	**Dominant**
Scenario 3: No between-treatment difference for cardiac morbidity or mortality, 1-year TH	–$6,218	0.001	**Dominant**
Scenario 4: No costs associated with AEs	–$24,030	0.096	**Dominant**
Scenario 5: AEs are double the base-case cost	–$22,885	0.096	**Dominant**

AE = adverse event; DFP = deferiprone; DFX = deferasirox; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; TH = time horizon.
Source: Manufacturer's pharmacoeconomic submission.[2]

The univariate sensitivity analysis indicated that the model was very sensitive to the daily dose of DFX, the daily dose of DFP, and the annual use of DFX. In each of these analyses, DFP lost dominance against DFX, and was associated with an incremental cost-utility ratio (ICUR) of approximately $500,000 or more (Figure 2).

FIGURE 2: TORNADO DIAGRAM PRESENTING RESULTS OF MANUFACTURER'S UNIVARIATE SENSITIVITY ANALYSES



DFP = deferiprone; DFX = deferasirox; NYHA = New York Heart Association; pts = patients; Tx = treatment; Yr = year.
Source: Manufacturer's pharmacoeconomic submission.[2]

The manufacturer's two-way sensitivity analysis tested different dose ranges for DFP and DFX. The analysis indicated that given the dose ranges for DFP (75 mg/kg to 100 mg/kg) and DFX (20 mg/kg to 30 mg/kg), DFP may not be less costly than DFX (Table 10).

TABLE 10: MANUFACTURER'S TWO-WAY SENSITIVITY ANALYSIS ASSESSING DOSE RANGES FOR DEFERIPRONE AND DEFERASIROX

		mg/kg (Deferiprone)							
		65	70	75	80	85	90	95	100
mg/kg (DFX)	20	$29,220	$44,333	$59,445	$74,558	$89,671	$104,783	$119,896	$135,009
	25	–$12,231	$2,881	$17,994	$33,107	$48,219	$63,332	$78,445	$93,557
	30	–$53,863	–$38,570	–$23,458	–$8,345	$6,768	$21,880	$36,993	$52,106
	35	–$95,135	–$80,022	–$64,909	–449,797	–$34,684	–$19,571	–$4,459	$10,654
	40	–$136,586	–$121,473	–$106,361	–$91,248	–$76,135	–$61,023	–$45,910	–$30,798

DFX = deferasirox.
Note: Red text indicates that DFP is cost-saving compared with DFX. Shading indicates the recommended dose range for DFP and DFX according to the product monographs (DFX may be initiated at 10 mg/kg in some patients).
Source: Adapted from Manufacturer's pharmacoeconomic submission.[2]

The manufacturer's probabilistic sensitivity analysis indicated that at WTP thresholds of $50,000 per quality-adjusted life-year (QALY) gained, the probability that DFP is cost-effective is 96.86%; this increases to 98.8% at $100,000 per QALY.

CADTH Common Drug Review Reanalyses

CADTH Common Drug Review (CDR) undertook reanalyses of DFP compared with DFX as per the manufacturer's base-case analysis, as well as an exploratory analysis for DFP compared with DFO. The CDR reanalyses of each are discussed in this section. Results are presented in Table 11 and Table 12. Lack of data restrained the comparison of DFP versus DFP-DFO.

Deferiprone versus Deferasirox

Uncertain comparative effectiveness of DFP versus DFX. No head-to-head comparison or rigorous network meta-analysis was available to compare DFP with DFX. The CDR clinical reviewers assessed the papers the manufacturer used to justify the assumption that data for DFO could be used as a proxy for DFX in the absence of data directly comparing DFP and DFX. The CDR clinical reviewers indicated that there is uncertainty regarding the comparative clinical effectiveness of DFP versus DFX. Therefore, as per the manufacturer's sensitivity analyses, CDR tested an assumption of no mortality and morbidity benefit for DFP over DFX on the manufacturer's base-case model. The results indicated that DFP was still associated with a minor QALY benefit and lower cost; thus, DFP dominated DFX (Table 11).

Comparative dosing of DFP and DFX may differ based on patient characteristics. The assumption that the daily doses (mg/kg) used in the base-case model were from the midpoints of each product monograph does not appear to be correct. The DFP product monograph indicates a dose range of 75 mg/kg/day to 100 mg/kg/day, while the DFX product monograph indicates a dose range of 10 mg/kg/day to 30 mg/kg/day for patients with transfusional iron overload (although patients inadequately controlled on 30 mg/kg/day DFX monotherapy may be considered for an increase to 40 mg/kg/day). The CDR clinical expert indicated that in practice, the average dose of DFX monotherapy ranged from 20 mg/kg/day to 40 mg/kg/day. The manufacturer assumed doses of 75 mg/kg/day for DFP and 30 mg/kg/day for DFX. Although clinical practice guidelines indicate the typical dose for DFP is 75 mg/kg/day, it is important to note that the clinical guidelines were published prior to DFP being approved for use in Canada.[27] Feedback from the CDR clinical expert indicated that the target dose for treatment depends on the patient's iron burden. If a patient's iron burden is lower, DFP monotherapy at

75 mg/kg/day is appropriate. However, in patients with a higher iron burden, DFP monotherapy at 100 mg/kg/day is appropriate. As seen in Table 10, the comparative doses of DFP and DFX have a substantial impact on the comparative costs. It is expected that at these higher iron burdens, patients would receive higher doses of DFX as well; thus, the dose of 100 mg/kg/day for DFP monotherapy was tested against DFX monotherapy at 30 mg/kg/day and 40 mg/kg/day. At lower iron burden levels, CDR undertook analyses comparing DFP monotherapy 75 mg/kg/day with DFX monotherapy of 20 mg/kg/day and 30 mg/kg/day.

In the opinion of the CDR clinical expert, the comparative doses were DFP monotherapy 75 mg/kg/day and DFX monotherapy 30 mg/kg/day in patients with lower iron burdens; and DFP monotherapy 100 mg/kg/day and DFX monotherapy 40 mg/kg/day in patients with higher iron burdens.

The results of the revised analyses can be seen in Table 11.

Frequency of monitoring visits may have been overestimated for both DFP and DFX. The CDR clinical expert indicated that the frequency of monitoring may have been overestimated; thus, CDR tested revised monitoring costs for DFP and DFX. As can be seen in Table 11, altering the frequency of monitoring does not have an impact on the base-case results.

The AE rate for hepatitis in DFX patients may have been overestimated. The manufacturer claimed that the AE rates were based on information provided in the product monographs. CDR could find no reference to the rate used in the manufacturer's submission (0.7%) in the product monograph. The product monograph indicated that one patient was diagnosed with subclinical hepatitis due to DFX overdose, which was cleared up after dose interruption.[20] CDR undertook a reanalysis assuming a 0% risk of hepatitis. As can be seen in Table 11, altering the rate of hepatitis does not affect the base-case results.

Availability of Canadian costs for AEs. Canadian costs for the treatment of agranulocytosis are available from the Alberta Interactive Health Data Application.[29] Based on CaseMix Group (CMG+) data from Alberta for 2013–2014 for all patients with agranulocytosis (CMG 633), the average cost was $9,770 — substantially higher than the value used in the economic model. As can be seen in Table 11, AE costs do not affect the base-case results.

Multi-way scenario analyses

CDR undertook a series of multi-way analyses based on the revised assumptions. The multi-way CDR reanalyses were undertaken considering four potential dosing scenarios based on iron burden with varying other parameters identified as limitations (Table 11): DFP monotherapy 75 mg/kg/day versus DFX monotherapy 20 mg/kg/day and DFX monotherapy 30 mg/kg/day (lower iron burden); and DFP monotherapy 100 mg/kg/day versus DFX monotherapy 30 mg/kg/day and DFX monotherapy 40 mg/kg/day (higher iron burden).

TABLE 11: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES AND SCENARIO ANALYSES (DEFERIPRONE VERSUS DEFERASIROX)

Reanalysis	DFP QALYs	DFX QALYs	QALY difference (DFP vs. DFX)	DFP costs	DFX costs	Cost difference (DFP vs. DFX)	ICUR (DFP vs. DFX)
Manufacturer's base case[a]	3.813	3.717	0.096	$230,275	$253,733	–$23,458	Dominant
1. DFX dose =	3.813	3.717	0.096	$230,275	$170,830	$59,445	$616,953/QALY

Reanalysis	DFP QALYs	DFX QALYs	QALY difference (DFP vs. DFX)	DFP costs	DFX costs	Cost difference (DFP vs. DFX)	ICUR (DFP vs. DFX)
20 mg/kg[b]							
2. DFP dose = 100 mg/kg[c]	3.813	3.717	0.096	$305,839	$253,733	$52,106	$540,776/QALY
3. DFP dose = 100 mg/kg; DFX dose = 40 mg/kg	3.813	3.717	0.096	$305,839	$336,636	–$30,797	Dominant
4. Revised monitoring costs	3.813	3.717	0.096	$229,749	$250,168	–$20,419	Dominant
5. Revised AE rate	3.813	3.723	0.090	$230,275	$253,712	–$23,437	Dominant
6. Revised AE costs	3.813	3.717	0.096	$230,700	$253,733	–$23,033	Dominant
7. No difference in mortality and morbidity	3.818	3.812	0.006	$230,275	$258,542	–$28,267	Dominant
Multi-way scenario analyses							
8. Multi-way analysis (4 to 6)	3.818	3.723	0.095	$230,174	$250,146	–$19,972	Dominant
9. Multi-way analysis (4 to 7)	3.818	3.819	–0.001	$230,174	$254,887	–$24,713	> $30 million/ QALY (DFX vs. DFP)
10. Multi-way analysis (1, 4 to 6)	3.818	3.723	0.095	$230,174	$167,243	$62,931	$662,504/QALY
11. Multi-way analysis (1, 4 to 7)	3.818	3.819	–0.001	$230,174	$170,413	$59,761	Dominated
12. Multi-way analysis (2, 4 to 6)	3.818	3.723	0.095	$305,737	$250,146	$55,591	$585,232/QALY
13. Multi-way analysis (2, 4 to 7)	3.818	3.819	–0.001	$305,737	$254,887	$50,850	Dominant
14. Combined analysis (3, 4 to 6)	3.818	3.723	0.095	$305,737	$333,050	–$27,313	Dominant
15. Combined analysis (3, 4 to 7)	3.818	3.819	–0.001	$305,737	$339,361	–$33,624	> $41 million/QALY (DFX vs. DFP)

AE = adverse event; DFP = deferiprone; DFX = deferasirox; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.
[a] The manufacturer's base case assessed 75 mg/kg/day DFP compared with 30 mg/kg/day DFX.
[b] Versus DFP 75 mg/kg/day.
[c] Versus DFX 30 mg/kg/day.

Exclusion of DFO alone or in combination as an appropriate comparator. The manufacturer assumed that DFO was not an appropriate comparator. Feedback from the CDR clinical expert and clinical practice guidelines indicated this assumption is incorrect; DFO in combination with DFX and DFP is also an appropriate comparator for DFP alone. Depending on the setting, DFO alone may potentially be a comparator. CDR undertook several exploratory analyses of DFP in comparison with DFO alone; lack of data prevented the comparison of DFP versus DFP and DFO combined.

Deferiprone versus Deferoxamine

Although the manufacturer's pharmacoeconomic report did not provide information for a comparative analysis of DFP versus DFO, the manufacturer's model did include the option to perform this analysis.

CDR was able to undertake an analysis comparing DFP versus DFO using the manufacturer's model structure and predetermined assumptions.

Uncertain comparative effectiveness of DFP versus DFO. The manufacturer's base-case data inputs were based on the assumption that data from patients receiving DFO could be used as a proxy for DFX; however, they were not from any of the three studies presented to CDR as pivotal studies. Thus, CDR undertook a series of analyses using DFO efficacy and safety data that the manufacturer had used as a proxy for DFX as well as from the pivotal study by Borgna-Pignatti et al.[30] and from the pivotal study by Piga et al.[10] (LA12-9907) (Table 12). Background information for each of these analyses has been briefly summarized here where required.

As noted in Table 6, the manufacturer used data from Piga et al.[10] and Maggio et al.[11] to determine the cardiac morbidity and mortality rates for DFX (using DFO as a proxy). These data indicated that there were no deaths for patients on DFP; they also indicated a cardiac mortality rate of ~4.8% for patients on DFO. The cardiac morbidity information suggested rates of 4% for DFP and 21% for DFO.

The observational study by Borgna-Pignatti et al.[30] was considered a pivotal study by the manufacturer, comparing DFP with DFO. The study reported that over the nine-year observation period, there were 52 cardiac events in the DFO group compared with none in the DFP group, and 24 deaths in the DFO compared with two in the DFP group. Fifteen of the 26 deaths were cardiac-related; all occurred while patients were receiving DFO. For context, the authors noted that 40% of these patients had previously received DFP; thus, CDR notes the potential for bias and confounding. AEs were based on the observational study; the authors reported that eight patients discontinued DFP due to neutropenia, one patient discontinued due to agranulocytosis, and one patient discontinued due to hepatitis C. However, the authors did not report any AEs other than cardiac events and mortality for DFO; thus, it was conservatively assumed that patients on DFO did not experience any AEs.

The observational study by Piga et al.[10] (LA12-9907) was considered a pivotal study by the manufacturer, comparing DFP with DFO. The study was one of those used by the manufacturer to populate the efficacy data in the model, providing data that populated the cardiac morbidity parameter. CDR undertook an analysis using cardiac mortality data reported in the paper as well; there were four deaths in the DFO group, compared with none in the DFP group. Three of the four deaths were cardiac-related, though all three patients had cardiac disease at the first assessment; all occurred while patients were receiving DFO. AEs were not presented in the published article; therefore, CDR conservatively assumed that AEs were 0% for each treatment.

This analysis was undertaken on the assumption that the utility values for patients receiving DFO as an infusion are lower than for patients receiving oral treatment (0.69), as per the results of multiple published utility studies that indicate that the utility value for oral treatments is approximately 0.84 while the utility value for patients receiving infusion treatment is 0.66.[12,19] CDR also updated DFO costs based on the Ontario Drug Benefit Formulary (November 2015)[31] and doses in line with the information sources. The base case assumes no administration costs, as per the other model regimens.

Dose of DFP may be underestimated and Canadian costs for AEs are available. CDR undertook analyses varying treatment dose and cost of AEs. Varying the dose of DFP significantly affect the ICUR, while revising AE costs does not (Table 12).

Dose of DFO may be underestimated. The available dose of DFO is reported to range from 20 mg/kg/day to 60 mg/kg/day, dosed between five and seven times per week. CDR undertook an analysis assuming the dose of DFP remained at 75 mg/kg/day while the dose of DFO increased to 60 mg/kg/day, seven times per week, to determine the yearly cost of DFO at the upper end. As can be seen in Table 12, altering the dose of DFO reduces the ICUR in CDR reanalysis 1.

Frequency of monitoring visits may have been overestimated for DFP, and monitoring visits have been updated and included for DFO. The CDR clinical expert indicated that the frequency of monitoring for DFP may have been overestimated (serum ferritin), while also indicating that monitoring for patients receiving DFO would include audiometry, ophthalmology, serum ferritin, serum creatinine, and liver function tests, and providing estimates of frequency for these parameters. Thus, CDR tested revised monitoring costs for DFP and DFO. As can be seen in Table 12, altering the frequency of monitoring does not affect the results from CDR reanalysis 1.

Testing the inclusion of administration costs for DFO. The CDR clinical expert indicated that since DFO is an infusion, the cost of administration should be included. The infusion costs in Canada are not well reported, particularly those specific to DFO. The UK paper by Karnon et al.[12] reported British infusion costs from 2007. When these costs were converted and inflated, the cost per infusion can be assumed to be approximately $60, which has been assumed by CDR to be the administration cost per infusion. As can be seen in Table 12, including administration costs for DFO reduces the ICUR from the ICUR in CDR reanalysis 1.

Multi-way analysis. CDR undertook an analysis combining reanalyses 1, 4, 5, 6, 7 and 8 (refer to Table 12. The multi-way CDR reanalysis indicated that DFP was associated with an ICUR of approximately $160,000 per QALY gained compared with DFO. However, CDR notes that there is substantial uncertainty with regards to the results due to the substantial uncertainty associated with the comparative efficacy and safety, and costs associated with the treatments. The range of ICURs from CDRs reanalyses was $77,000 per QALY to $362,000 per QALY.

TABLE 12: SUMMARY OF CDR REANALYSES (DEFERIPRONE VERSUS DEFEROXAMINE)

Reanalysis	DFP QALYs	DFO QALYs	QALY Difference (DFP vs. DFO)	DFP Costs	DFO Costs	Cost Difference (DFP vs. DFO)	ICUR (DFP vs. DFO)
1. Comparative effectiveness: base-case analysis	3.813	3.076	0.737	$230,275	$38,308	$191,967	$260,367/ QALY
2. Comparative effectiveness: Borgna-Pignatti[a]	6.259	4.975	1.284	$377,662	$62,349	$315,313	$245,495/ QALY
3. Comparative effectiveness: Piga (LA12-9907)[b]	3.814	3.033	0.781	$225,740	$36,971	$188,769	$241,938/ QALY
The following two analyses have been undertaken using assumptions from reanalysis 1							
4. Deferiprone dose = 100 mg/kg	3.813	3.076	0.737	$305,839	$38,308	$267,531	$362,854/ QALY
5. Revised AE costs	3.813	3.076	0.737	$230,700	$38,308	$192,392	$260,943/ QALY
The following analyses have been undertaken using efficacy and safety data from the manufacturer's base case (Maggio et al.[11] and Piga et al.)[10]							
6. Deferoxamine dose = 60 mg/kg[c]	3.813	2.925	0.888	$230,275	$63,294	$166,981	$188,020/ QALY

Reanalysis	DFP QALYs	DFO QALYs	QALY Difference (DFP vs. DFO)	DFP Costs	DFO Costs	Cost Difference (DFP vs. DFO)	ICUR (DFP vs. DFO)
7. Revised monitoring costs[d]	3.813	3.076	0.737	$229,749	$38,695	$191,054	$259,127/ QALY
8. Revised administration costs[e]	3.813	3.076	0.737	$230,275	$117,542	$112,733	$152,901/ QALY
Multi-way analysis							
9. Multi-way analysis (1, 6 to 8)	3.813	2.925	0.888	$229,749	$161,387	$68,362	$76,976/ QALY
10. Combined analysis (1, 4 to 8)	3.813	2.925	0.888	$305,737	$161,387	$144,350	$162,538/ QALY

AE = adverse event; DFO = deferoxamine; DFP = deferiprone; DFX = deferasirox; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; vs. = versus.

[a] Time horizon was extended to 9 years per the follow-up period. No average dose of DFP or DFO was provided in Borgna-Pignatti et al.;[30] thus, the average dose of DFP from the base case was used (75 mg/kg), and the average dose of DFO was assumed as per the base case from LA16-0102 (43 mg/kg 5.7 days a week).[8]

[b] The average dose of DFP was 73.7 mg/kg and the average dose of DFO was 39.2 mg/kg 6 days a week. AEs were set to 0%, as they were not reported in the study.[10] CDR notes that the low range for the dose is 25 mg/kg, which is well below the recommended dose in the product monograph (75 mg/kg to 100 mg/kg). This likely skews the average dose lower than would be used in Canadian clinical practice.

[c] The DFO dose was assumed to increase to 60 mg/kg 7 days a week. The average dose of DFP was 75 mg/kg, as per the base case.

[d] Monitoring costs for DFO were assumed to consist of the following: audiometry, ophthalmology, serum ferritin, serum creatinine, and liver function tests.

[e] The administration cost was conservatively assumed to be $60 per infusion. As the manufacturer calculated that patients receiving DFO had 296 infusions per year, this had a substantial impact on the results.

The manufacturer also indicated that the RCT published by Pennell et al.[8] (LA16-0102) should be considered a pivotal study. CDR was unable to undertake an analysis of DFP versus DFO based on the study, as it did not capture cardiac morbidity and cardiac mortality. CDR noted that a higher average dose of DFP was seen in that study compared with LA12-9907 (93 mg/kg versus 74 mg/kg).

CDR identified other limitations that were not tested due to the model structure, lack of usable sources, or substantial uncertainty in the values used:

- CDR was unable to test the impact of appropriate Canadian costs associated with each of the different AEs included in the model; CDR was only able to locate costs for agranulocytosis and neutropenia. However it was unclear based on the reporting as to whether these were completely appropriate for use. There is substantial uncertainty associated with using international data and costs to estimate Canadian costs and resource use. However, in the absence of Canadian evidence, it does provide some form of estimate of the costs.
- Patients with thalassemia receiving regular transfusions require lifelong treatment. Therefore, a longer time horizon may have been more appropriate; however, this would have increased the uncertainty regarding the extrapolation of data and potential for treatment waning. Given the uncertainty around the model structure and comparisons, it was determined that testing this parameter would only increase the uncertainty in the results. Therefore, an analysis of this parameter was not undertaken.

REFERENCES

1. Ferriprox (deferiprone): Tablets 500 mg and 1000 mg; Oral solution 100 mg/mL [product monograph]. Toronto (ON): ApoPharma Inc.; 2015 Jan 22.
2. Pharmacoeconomic evaluation. In: CDR submission: Ferriprox (deferiprone), 1000 mg tablets and 100 mg/mL oral solution. Company: ApoPharma Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): ApoPharma Inc.; 2015 Sep.
3. Bentley A, Gillard S, Spino M, Connelly J, Tricta F. Cost-utility analysis of deferiprone for the treatment of beta-thalassaemia patients with chronic iron overload: a UK perspective. PharmacoEconomics [Internet]. 2013 Sep [cited 2015 Oct 15];31(9):807-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3757270/pdf/40273_2013_Article_76.pdf
4. Ferriprox (deferiprone) [Internet]. London: European Medicines Agency; 2015. [cited 2015 Dec 17]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000236/human_med_000789.jsp&mid=WC0b01ac058001d124
5. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Exjade (deferasirox) tablets for oral suspension [Internet]. In: Exjade label. Rockville (MD): FDA; 2010 Jan [cited 2015 Dec 17]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021882s010lbl.pdf.
6. Schedule of benefits for physician services under the Health Insurance Act [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2015. [cited 2015 Oct 16]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html
7. Ontario Health Insurance (OHIP) schedule of benefits and fees. Schedule of benefits of laboratory services [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2013 May 30. [cited 2015 Oct 16]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/lab_mn.html
8. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood [Internet]. 2006 May 1 [cited 2015 Oct 30];107(9):3738-44. Available from: http://www.bloodjournal.org/content/bloodjournal/107/9/3738.full.pdf
9. Luangasanatip N, Chaiyakunapruk N, Upakdee N, Wong P. Iron-chelating therapies in a transfusion-dependent thalassaemia population in Thailand: a cost-effectiveness study. Clin Drug Investig. 2011;31(7):493-505.
10. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica [Internet]. 2003 May [cited 2015 Oct 29];88(5):489-96. Available from: http://www.haematologica.org/content/88/5/489.full-text.pdf+html
11. Maggio A, Vitrano A, Capra M, Cuccia L, Gagliardotto F, Filosa A, et al. Improving survival with deferiprone treatment in patients with thalassemia major: a prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. Blood Cells Mol Dis. 2009 May;42(3):247-51.
12. Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. Curr Med Res Opin. 2008 Jun;24(6):1609-21.

13. Ossa D, Briggs A, Tafesse E, Iloeje U, Mukherjee J, Lozano-Ortega G, et al. Impact on quality of life of health states induced by chronic hepatitis B infection: estimates from uninfected and infected persons in the UK [abstract]. Value Health [Internet]. 2005 [cited 2015 Nov 16];8(6):A60. Available from: http://www.valueinhealthjournal.com/article/S1098-3015(10)67323-8/pdf (Presented at 8th Annual European Congress of the International Society for Pharmacoeconomics & Outcomes Research (ISPOR); 2005 Nov 6-8; Florence, Italy).
14. Priest VL, Begg EJ, Gardiner SJ, Frampton CM, Gearry RB, Barclay ML, et al. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. PharmacoEconomics. 2006;24(8):767-81.
15. Perlis RH, Ganz DA, Avorn J, Schneeweiss S, Glynn RJ, Smoller JW, et al. Pharmacogenetic testing in the clinical management of schizophrenia: a decision-analytic model. J Clin Psychopharmacol. 2005 Oct;25(5):427-34.
16. Cost-effectiveness analysis registry [Internet]. Boston (MA): Tufts Medical Center; 2015. [cited 2015 Nov 10]. Available from: https://research.tufts-nemc.org/cear4/
17. Yacobovich J, Stark P, Barzilai-Birenbaum S, Krause I, Pazgal I, Yaniv I, et al. Acquired proximal renal tubular dysfunction in beta-thalassemia patients treated with deferasirox. J Pediatr Hematol Oncol. 2010 Oct;32(7):564-7.
18. Ontario Ministry of Health and Long-Term Care. Drug benefit prices (DBPs) for products reimbursed under the EAP [Internet]. Toronto: The Ministry; 2015. [cited 2015 Oct 16]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx
19. Osborne RH, De Abreu LR, Dalton A, Houltram J, Dowton D, Joshua DE, et al. Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. Value Health. 2007 Nov;10(6):451-6.
20. Exjade (deferasirox): Dispersible tablets for oral suspension 125 mg, 250 mg, or 500 mg [product monograph] [Internet]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2015 Feb 11. [cited 2015 Oct 16]. Available from: http://www.novartis.ca/en/products/pharmaceuticals/index.shtml?letter=e
21. Desferal (deferoxamine mesylate for injection, Novartis Std.): Lyophilized powder 500 mg/vial and 2.0/vial [product monograph]. Dorval [QC]: Novartis Pharmaceutical Canada Inc.; 2015 Oct 2.
22. pms-Deferoxamine (deferoxamine mesylate for injection): lyophilized powder 500 mg/vial 2.0 g/vial [product monograph]. Montreal (QC): Pharmascience; 2012.
23. Berdoukas V, Chouliaras G, Moraitis P, Zannikos K, Berdoussi E, Ladis V. The efficacy of iron chelator regimes in reducing cardiac and hepatic iron in patients with thalassaemia major: a clinical observational study. J Cardiovasc Magn Reson [Internet]. 2009 [cited 2015 Oct 22];11:20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713224/pdf/1532-429X-11-20.pdf
24. Pepe A, Meloni A, Capra M, Cianciulli P, Prossomariti L, Malaventura C, et al. Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison determined by quantitative magnetic resonance imaging. Haematologica [Internet]. 2011 Jan [cited 2015 Oct 22];96(1):41-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012763/pdf/0960041.pdf
25. Clinical Study Report: LA16-0102. Randomized trial comparing the relative efficacy of deferiprone to that of deferoxamine in removing excess cardiac iron in thalassemia major patients [**CONFIDENTIAL** internal manufacturer's report]. Toronto (ON): ApoPharma; 2004 Oct 13.
26. Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanello R, et al. Cardiovascular function and treatment in beta-thalassemia major: a consensus statement from the American Heart Association. Circulation [Internet]. 2013 Jul 16 [cited 2015 Oct 30];128(3):281-308. Available from: http://circ.ahajournals.org/content/128/3/281.full.pdf+html

27. Anemia Institute for Research & Education, Thalassemia Foundation of Canada. Guidelines for the clinical care of patients with thalassemia in Canada [Internet]. Vaughan (ON): Thalassemia Foundation of Canada; 2009. [cited 2015 Nov 16]. Available from: http://www.thalassemia.ca/wp-content/uploads/Thalassemia-Guidelines_LR.pdf

28. Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value Health. 2010 Dec;13(8):922-33.

29. Interactive health data application (IHDA) [Internet]. Edmonton: Alberta Health. Health costing; 2015 [cited 2015 Dec 8]. Available from: http://www.ahw.gov.ab.ca/IHDA_Retrieval/selectCategory.do

30. Borgna-Pignatti C, Cappellini MD, De SP, Del Vecchio GC, Forni GL, Gamberini MR, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood [Internet]. 2006 May 1 [cited 2015 Oct 30];107(9):3733-7. Available from: http://www.bloodjournal.org/content/bloodjournal/107/9/3733.full.pdf

31. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2015 Sep 30. [cited 2015 Oct 16]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/