CADTH

CADTH TECHNOLOGY REVIEW

Hemin for Injection (Panhematin): Budget Impact Analysis

Service Line:	Technology Review
Issue:	24
Publication Date:	October 2019
Report Length:	25 Pages

CADTH

Authors: Samantha Verbrugghe; Shehzad Ali; Karen Lee.

Cite as*: Hemin for Injection (Panhematin): Budget Impact Analysis*. Ottawa: CADTH; 2019 Oct. (CADTH Technology Review; no. 24).

Acknowledgments: CADTH would like to acknowledge various participants in the development of this report: Lorna Adcock (CADTH) for information services support; and Sarah McDonald (CADTH) for project management support.

ISSN: 2369-7385

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

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

Contact **requests@cadth.ca** with inquiries about this notice or legal matters relating to CADTH services.

CADTH

Table of Contents

Tables

Abbreviations

AIP	acute intermittent porphyria
CBS	Canadian Blood Services
SAP	Special Access Programme

Executive Summary

In Canada, patients requiring treatment for severe acute intermittent porphyria (AIP) attacks were previously managed with human hemin, either Panhematin or Normosang, through Health Canada's Special Access Programme (SAP).

Health Canada approved Panhematin for the amelioration of recurrent attacks of AIP temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.[1] The manufacturer submitted a price of [redacted] per 268 mg vial of Panhematin. Based on the manufacturer's analysis, but assuming coverage is limited only to the indicated population, CADTH analysis suggested funding Panhematin would cost [redacted] in the first year, increasing to [redacted] by year 3. However, the manufacturer reported that 18 patients received 215 vials of Normosang through the SAP in 2017, which, at the submitted price and assuming similar utilization, would result in a total cost [redacted] if Panhematin had been used.[2] This is substantially higher than the CADTH estimates, likely because access under the SAP was not restricted to female patients with AIP attacks related to menstrual cycles.

When considering a population including all women with AIP attacks requiring treatment, CADTH's estimate increased to $[redacted]million per year for the first three years, with 32 patients treated per year. When a population including all patients with AIP attacks requiring treatment, regardless of gender, was considered, CADTH's estimate increased to $[redacted] million per year for the first three years, with 41 patients treated per year. This scenario is consistent with the views of the clinical experts consulted by Canadian Blood Services (CBS); i.e., Panhematin is likely to be used in any patient with AIP where hemin therapy is deemed appropriate, without restriction because of gender or relation to the menstrual cycle. Also, CADTH's estimated figure of $[redacted] million per year is similar, though slightly lower, to that estimated by the manufacturer.

There are substantial uncertainties with the analysis, especially pertaining to the generalizability of prevalence data from a European to a Canadian population, the potential for off-label use, and the reliance on unpublished utilization inputs from the manufacturer without adequate explanation of data source or methodology. A series of sensitivity analyses were run on each of the three populations of AIP patients to test each assumption, leading to a range of estimates between $[redacted] per year to almost $[redacted]million per year.

There is also the potential for Panhematin to be used in a wider population of hepatic porphyria patients — those with variegate porphyria or hereditary coproporphyria, in addition to those with AIP. Also, Panhematin might be used prophylactically in patients with AIP with chronic or very severe symptoms, as suggested by the experts consulted by CBS. These possibilities were not formally assessed because of a lack of data, but if access to Panhematin was provided more broadly in practice, it would significantly increase the budget impact.

Note that this analysis does not consider the clinical benefits associated with Panhematin treatment. The approach adopted is based on the manufacturer's submission of a budget impact analysis, which does not estimate potential gains in patient quality of life, potential costs associated with treatment-emergent adverse events, or the potential savings should the use of Panhematin reduce other immediate or downstream health care costs. To adequately address any clinical or quality of life benefit to Panhematin therapy in patients with AIP, the manufacturer would have needed to submit a formal economic evaluation allowing assessment of the incremental costs per benefit obtained.

Background Information

Acute porphyrias are a group of rare metabolic disorders caused by abnormal functioning of heme biosynthesis enzymes, leading to the buildup of heme precursors. The current review focuses on acute intermittent porphyria (AIP) — the most common of the acute porphyrias in European populations, particularly those in Northern Europe and the UK;[3] there are no Canadian epidemiological studies that estimate the prevalence of porphyrias. Like other porphyrias, AIP is an autosomal dominant disorder with low penetrance; i.e., most heterozygotes will remain asymptomatic throughout their lives.[4] When symptoms do manifest, they usually present as intermittent attacks that may be life-threatening and typically begin after puberty. AIP is more common in women than men because of hormonal differences.[3,4]

Acute attacks typically present with severe but non-specific abdominal pain, which may be accompanied by pain in other areas, as well as nausea, vomiting, constipation, hypertension, tachycardia, anxiety, agitation, depression, confusion, hallucinations, or seizures.[3,4] Progesterone increases heme catabolism and thus some women have attacks related to their menstrual cycle, or upon initiating birth control or other synthetic estrogen or progesterone therapies. Other changes such as certain medications, alcohol, stress, infection, or caloric restriction may also increase the chances of an attack.[4]

Current Treatment Options

Minor attacks may be treated with a high carbohydrate diet because of the inhibitory effect of glucose on the production of heme precursors, and supportive measures for symptoms such as opioids for pain. For more severe attacks, immediate treatment with an infusion of human hemin is preferred.[3]

Prior to July 2018, no hemin products were approved for use in Canada, although two products are available outside of Canada: Panhematin (lyophilized human hemin — the product being reviewed) is available in the US, while Normosang (heme arginate) is available in Europe.[3]

Hemin for Injection (Panhematin)

Panhematin (hemin for injection) is indicated for the amelioration of recurrent attacks of AIP temporally related to the menstrual cycles in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.[1] It is an enzyme inhibitor derived from processed red blood cells, and is the first hemin product to be approved by Health Canada, although some patients have been able to access treatment with Panhematin or Normosang through the Health Canada Special Access Programme (SAP). However, patients responding to a Canadian Association for Porphyria survey indicated that access was not consistent or adequate across the country.[5]

Panhematin is supplied as a sterile, lyophilized powder in single-dose vials at a submitted price of [redacted]. Each vial contains 268 mg of Panhematin which, after reconstitution with 48 mL of sterile water, may be administered through intravenous infusion over a period of at least 30 minutes via a separate line, and provides approximately 261 mg of hematin at 5.4 mg/mL. It should be noted that this vial is identical in content, quality, and quantity to that available in the US; however, because of differences in label requirements between regulatory agencies, the vial is interpreted by the FDA as including 350 mg of hemin, while

Health Canada considers it to hold 268 mg. At the recommended dose of 2.3 mg/kg/day to 3.1 mg/kg/day, a vial contains enough hematin (261 mg when reconstituted) for an 84 kg person at the upper end of the recommended dose.

The product contains no preservatives and any excess of the drug must be discarded.[1] To increase stability and to reduce side effects associated with the formation of degradation products,[6] Panhematin is sometimes reconstituted with 132 mL of 25% human serum albumin rather than with sterile water.

Comparative Efficacy and Safety

Due to the rarity of AIP, only one double-blind, placebo-controlled trial has been conducted on the use of hemin to treat AIP attacks,[7] which showed a positive but statistically non-significant benefit in the relief of pain. This lack of significance has been attributed to a delay in treatment within the study (patients were randomized two days after hospital admission), as well as its very small sample size (n = 12).[3] Larger, uncontrolled[8] or observational studies[9] have demonstrated the benefit and safety of hemin use in hepatic porphyria patients to the satisfaction of the experts consulted by Canadian Blood Services (CBS), and guidelines advocate its use for patients with moderate-to-severe attacks, as it is believed to speed the resolution of symptoms, decrease the length of hospital stays, and lower the incidence of complications such as neuropathy or seizures.[3,10]

There are no clinical trials comparing Panhematin with Normosang — the comparative efficacy of these blood products is unknown.

Potential for Off-Label Use

Based on feedback from clinical experts consulted by CBS, it is very likely that Panhematin will be used for any patient with AIP requiring hemin therapy, regardless of gender; i.e., beyond the indicated population of women with recurrent attacks temporally related to their menstrual cycles. There is also the potential that Panhematin may be used for patients with other hepatic porphyrias; i.e., hereditary coproporphyria (HCP) or variegate porphyria, as well as prophylactically for those with chronic or recurrent symptoms.

Policy and Ethical Issues

While the Health Canada indication for Panhematin is for recurrent attacks related to the menstrual cycle in susceptible women, the experts consulted by CBS found this indication to be too restrictive and noted that there is evidence that Panhematin benefits patients with AIP attacks regardless of gender or relation to menstrual cycle.[11] It is likely that restriction by gender or in relation to menstrual cycle in patients who are otherwise deemed likely to benefit from hemin treatment may be seen as unethical.

Panhematin and Normosang have previously been available only through the SAP in Canada. A recent survey, conducted by the Canadian Association for Porphyria in 2016 found that only half of patients (eight of 16) told by a physician that they should receive hemin therapy were able to access it.[5]

Objectives

This report aims to assess, from the Canadian health care system perspective (excluding Quebec), the budgetary impact of reimbursing Panhematin over a three-year period for the amelioration of recurrent and sporadic attacks of AIP temporally related to the menstrual cycle of susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.

Because of the likelihood of significant off-label use, as described in section 1.4, the analysis also explored the budgetary impact of reimbursing Panhematin for all AIP attacks in women, regardless of temporal relation to their menstrual cycle, as well as AIP attacks in all patients regardless of gender.

The safety and efficacy of Panhematin has not been established in pediatric patients (defined in the product monograph as those less than 16 years of age[1]); thus, the use of Panhematin in the pediatric population was not considered.

Budget Impact Analysis

Approach

The manufacturer provided a budget impact analysis to assess the national budgetary implications of reimbursing Panhematin in Canada.[2] A prevalence-based approach was taken using a three-year analysis time frame — reference year: 2018; year 1: 2019; year 2: 2020; year 3: 2021. A national perspective was applied; however, Quebec was excluded from the analysis, as blood products for patients in the province are provided by Héma-Québec rather than CBS.

As part of the review, the methods and assumptions of the manufacturer's budget impact analysis were assessed, and where possible validated, and any further assessment of uncertainty considered in reanalyses.

The manufacturer did not provide a written report detailing the background, assumptions, and reasoning behind their modelling decisions. This limited CADTH's ability to evaluate and fully understand the rationale of aspects of the model.

Methods

The manufacturer's base-case analysis (labelled as its "estimated analysis") estimates the number of AIP patients in Canada with attacks requiring hemin treatment over a three-year time horizon. The manufacturer did not limit the population to the Health Canada indication of "to ameliorate recurrent attacks of AIP temporally related to the menstrual cycle in susceptible women." Assumptions made by the manufacturer for use in the model can be found in Table 5.

Model Inputs and Estimated Number of Treated Cases

The manufacturer assumed the prevalence and incidence of AIP in Canada based on a 2013 study by Elder et al.[12] conducted in a European population. Table 1 summarizes the key model parameters used in the manufacturer's submission.

Table 1: Manufacturer's Prevalence, Incidence, and Cost Inputs

Statistic	Estimate	Source
Prevalence of manifest AIP (having had at least one attack) per 100,000 population, irrespective of gender	0.54	Elder et al. (2013)[12]
Proportion of patients with manifest AIP with recurrent attacks	5.3%	Elder et al. (2013)[12a]
Proportion of patients with manifest AIP without recurrent, but with sporadic, attacks	20%	Assumption, based on an unspecified 1-in-5 statistic
Number of attacks per year for patients who had recurrent attacks	4	Definition of recurrent attacks, Elder et al. (2013)[12]
Number of attacks per year for patients who had sporadic attacks	1	Assumption supported by manufacturer-held *data on file*
Incidence (new cases) of symptomatic AIP per million population, per year	0.13	Elder et al. (2013)[12]
Proportion of incident AIP requiring hospitalization	82%	Elder et al. (2013)[12]
Cost per 268 mg vial of Panhematin	$[redacted]	Provided by manufacturer[2]
Number of Panhematin vials used per attack	4	Assumes one vial per day for 4 days[2]
Cost of treating one attack	$[redacted]	Four times vial cost

AIP = acute intermittent porphyria.

[a] While the Elder et.al (2013)[12] study reported that 5.3% of female manifest AIP patients would experience recurrent attacks, the manufacturer's submission applied this figure to the whole patient population, regardless of gender.

Source: Adapted from the manufacturer's economic submission.[2]

To summarize, based on prevalence and incidence data from Elder et al. (2013)[12] (Table 1), the manufacturer estimated that there are 154 prevalent manifest AIP patients in Canada (excluding Quebec) in 2018 (Canadian population, excluding Quebec: 28,557,550). Of these, 5.3% (eight patients) would have recurrent attacks (four attacks per year) requiring treatment, while an additional 20% (31 patients) would have sporadic attacks (one attack per year) requiring treatment. Additionally, also based on Elder et al. (2013)[12], the manufacturer assumed 0.13 newly diagnosed AIP patients (i.e., incident symptomatic cases) per million people (four incident cases in Canada outside of Quebec); of these, 82% would require hospitalization and are assumed to require treatment with Panhematin. Based on these inputs, the manufacturer's base-case analysis estimates the total number of treated patients and treated attacks, which are presented in Table 2.

In summary, in year 3, an estimated 43 patients with AIP would be treated for 68 acute attacks per year.

Table 2: Manufacturer's Estimate of Patient Numbers Based on Estimated Prevalence and Incidence

	Baseline 2018	Year 1 2019	Year 2 2020	Year 3 2021
Population of Canada, excluding Quebec, projected	28,557,550	28,803,145	29,050,852	29,300,689
Prevalent manifest AIP estimate				
Number of prevalent AIP patients	154	156	157	158
Prevalent AIP with recurrent attacks (5.3%)	8	8	8	8
Prevalent AIP with sporadic attacks	31	31	31	32
Incident symptomatic AIP estimate				
Incident symptomatic AIP patients	4	4	4	4
Incident symptomatic AIP patients requiring hospitalization	3	3	3	3
Total estimated number of patients who may be treated with Panhematin	42	42	43	43
Total estimated number of treated attacks which may be treated with Panhematin	67	67	68	68
Average number of attacks per patient	1.58	1.58	1.58	1.58

AIP = acute intermittent porphyria.

Source: Adapted from the manufacturer's economic submission.[2] Calculated figures are rounded to the nearest whole patient or attack and may not precisely add up to the presented totals. Patients were not restricted by gender. The total estimated number of patients who may be treated with Panhematin includes prevalent patients with recurrent attacks, prevalent patients with sporadic attacks, and incident patients requiring hospitalization.

Manufacturer's Estimated Budget Impact

Manufacturer's Base-Case Analysis

The manufacturer estimated that, based on the prevalence and incidence rates previously presented, if Panhematin is reimbursed within Canada for the treatment of AIP attacks, the budget impact is likely to be approximately $[redacted] million [redacted] first three years (see Table 3).

Table 3: Manufacturer's Results: Number of Vials Used Per Year and Their Budget Impact Based on Estimated Prevalence Data

	Baseline 2018	Year 1 2019	Year 2 2020	Year 3 2021
Number of Panhematin vials used[a]				
For patients with recurrent attacks (i.e., 8 patients with 4 attacks each per year)	131	132	133	134
For patients with sporadic attacks (i.e., 31 patients with 1 attack each per year)	123	124	125	127
For hospitalized incident patients (i.e., 3 patients with 1 attack each)	12	12	12	12
TOTAL vials per year estimate	**266**	**269**	**271**	**273**
Cost per Panhematin vial	[redacted]			
Cost of treating AIP attacks				
Cost of prevalent patients with recurrent attacks	[redacted]	[redacted]	[redacted]	[redacted]
Cost of prevalent patients with sporadic attacks	[redacted]	[redacted]	[redacted]	[redacted]
Cost of hospitalized incident patients	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL predicted cost per year	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL predicted cost in first three years		**$6,861,605**		

AIP = acute intermittent porphyria.

Note: the manufacturer's analysis assumes that 5.3% of prevalent patients with manifest AIP will have recurrent attacks. This is based on the estimate reported in Elder, 2013[12] for women with AIP who had recurrent attacks. However, the manufacturer applied the same estimate (i.e., 5.3%) to all patients in the analysis without restriction by gender. This resulted in higher budget impact than would be estimated if the lower rate of recurrence reported in Elder 2013 (i.e., 2.8%) was used for men.

[a] The analysis assumed that four vials are used to manage each attack.

Source: Adapted from the manufacturer's economic submission.[2] Patients were not restricted by gender. Reported numbers of patients, attacks, and vials are rounded to the nearest whole number and may not precisely add up to the presented totals.

Manufacturer's Sensitivity Analysis

Whereas the manufacturer's model was flexible enough to allow sensitivity analyses based on alternate parameter values, these sensitivity analyses were not reported.

The manufacturer did, however, included a scenario labelled "actual," which included the number of patients treated with hemin — in this case Normosang — under the SAP in 2017, excluding Quebec, as well as the number of vials used to treat them. The manufacturer reported that 18 Canadian patients were treated with 215 vials of Normosang. As both Normosang and Panhematin require one vial per patient, per day of treatment, due to instability of the reconstituted products,[1,13] utilization of the two is likely to be similar. Assuming the same number of Panhematin vials used in place of Normosang, at a price of $[redacted] per 268 mg vial, the total cost of treating Canadian patients (excluding those in Quebec) in 2017 would have been $[redacted] million (see Table 4). It is unclear from the manufacturer's model whether or not all 18 patients receiving hemin in 2017 specifically had AIP as opposed to one of the other hepatic porphyrias, nor is it clear what proportion of patients were women and what proportion had recurrent and sporadic attacks. As a result, manufacturer's prevalence-based estimates in Table 3 are not directly comparable to the SAP-based estimates in Table 4. It should also be noted that, as not all eligible patients had access to hemin through SAP, the "actual" budget impact is lower than the estimated figures in Table 3 (which was based on the entire population).

The manufacturer projected that, should Panhematin be reimbursed through CBS, then a total of 30 patients would be treated in 2019, rising to 50 by 2021. The rationale or data

behind this projection was not reported. The manufacturer assumed that the most severe patients, those most likely to have higher rates of recurrent attacks, are already receiving treatment through SAP, and thus the mean number of attacks per patient, per year, would decrease as the product becomes more widely available to patients. The manufacturer estimated that the average number of attacks would decrease to 1.35 per patient, per year, in 2021. Whereas the direction of this assumption appears reasonable, the methods used to derive the magnitude of the projected decrease were not reported.

CADTH notes that the number and duration of AIP attacks as well as access to treatment may vary from one year to another; as a result, the number of vials reimbursed through SAP (and their cost) may be different across year. Therefore, prevalence-based estimates (as reported in Table 3) are preferred over SAP-based figures (Table 4) for estimating expected budget impact.

Table 4: Manufacturer's Projected Use and Budget Cost Based on 2017 Hemin Utilization

	Actual	Manufacturer's Projection		
	2017 Baseline	Year 1 2019	Year 2 2020	Year 3 2021
Patients treated with hemin in Canada	18	30	45	50
Number of vials used	215	NA	NA	NA
Average units per patient per year	11.94	NA	NA	NA
Average number of attacks per patient per year	2.99	2.20	1.50	1.35
Cost of Panhematin treatment[a]	[redacted]	[redacted]	[redacted]	[redacted]

NA = not applicable.

[a] Example calculation for 2019: 30 projected patients, having an average of 2.20 attacks per year, using 4 vials per attack, at a cost of [redacted] per vial. The price of Panhematin was used in the calculations, which further assumed the equivalent utilization of Panhematin and Normosang, on a vial-to-vial basis.

Source: Manufacturer's Economic Submission.[2] According to the manufacturer, all hemin supplied through the SAP in 2017 was Normosang.

CADTH Reanalysis

CADTH Analysis Based on Restriction to the Indicated Population

The manufacturer made a number of assumptions in its model, which are outlined in Table 5. As a first step to understanding the potential use of Panhematin in Canada, CADTH conducted a reanalysis limiting the use of Panhematin to the indicated (on-label) population of women with AIP attacks related to their menstrual cycles; assumptions used to estimate this population are outlined in Table 5, along with other more realistic patient populations explored (i.e., all AIP attacks in women, and in all patients with AIP regardless of gender), as well as a number of sensitivity analyses meant to explore uncertainty around other modelling assumptions.

Table 5: Assumptions Used in Manufacturer's Budget Impact Analysis and Revised in CADTH's Reanalyses

Manufacturer Base-Case Assumption (as Provided in Its Budget Impact Analysis)	Revised Assumption for CADTH Reanalysis Restricted to Indicated Population	Additional CADTH Analyses
Analysis includes all patients with AIP attacks	Analysis was limited to female AIP patients (= 76% of total AIP patients, based on Elder et. al [2013])[12]. The population was further restricted to women most likely to have menstrual cycle-related AIP attacks (i.e., 48% of female AIP patients, based on Bonkovsky et al. [2014]).[9]	Scenario analyses based on the inclusion of: • all female patients with AIP attacks requiring treatment • all patients with AIP attacks requiring treatment, regardless of gender. The sensitivity analyses subsequently listed were also conducted based on these scenarios.
Prevalence of AIP is 0.54 per 100,000	Prevalence of women with AIP = 0.41 per 100,000 population (calculation: 0.54 AIP patients per 100,000 x 76% of AIP patients are women)	95% CI[a] limits from Elder et. al (2013): 0.45 to 0.63 per 100,000 multiplied by 76% for women Two of the countries reported in Elder et al. (2013), Sweden and Switzerland, had prevalence rates of AIP, which were significantly higher (2.3 and 0.99 per 100,000, respectively) than the overall prevalence and 95% CI limit; these higher prevalence rates were tested in sensitivity analyses.
Analysis assumes all incident AIP patients who require hospitalization will be treated with Panhematin	No change	None
5.3% of manifest AIP patients have recurrent attacks; the manufacturer used the proportion of female AIP patients having recurrent attacks reported in Elder et al. (2013), but applied it to all AIP patients, without regard for gender, in the model	5.3% of female AIP patients have recurrent attacks (i.e., the same as the manufacturer's analysis but limiting the population to females, only).[12] 48% of female AIP patients with attacks have attacks related to menstruation[9]	95% CI limits from Elder et al. (2013): 4.0% and 6.9% Additionally, alternate proportions of women with attacks related to their menstrual cycles are explored; i.e., 25% and 75%. When included in reanalyses, 2.8% of male patients with AIP were reported to have recurrent attacks.[12]
20% of manifest AIP patients who do not have recurrent attacks will have sporadic attacks (based on assumption without a clear source)	No change	15% and 25% of patients with manifest AIP have a sporadic attack per year
Patients are assumed to have four days of treatment per attack, using four vials of Panhematin (i.e., one vial per day)	No change	Patients are assumed to require treatment for: • 3 days (= 3 vials), the recommended minimum • 6 days (= 6 vials) • 14 days (= 14 vials), the recommended maximum

Manufacturer Base-Case Assumption (as Provided in Its Budget Impact Analysis)	Revised Assumption for CADTH Reanalysis Restricted to Indicated Population	Additional CADTH Analyses
Only cost of drug included	No change	Included estimated cost of infusion and lab tests associated with Panhematin treatment
Assumes Panhematin will be reconstituted with sterile water, as directed in the product monograph	No change	Assumes Panhematin will be reconstituted with 132 mL of 25% human serum albumin to prolong stability[6]
Assumes that patients will use one 268 mg vial of Panhematin per day of treatment, with excess medication wasted	No change	None

AIP = acute intermittent porphyria; CI = confidence interval.

[a] 95% CI is the 95% confidence interval reported in the source data.

The initial CADTH analysis estimates the population of patients who would require Panhematin if availability was restricted to its indication: recurrent attacks in women with AIP temporally related to the menstrual cycle. It should be noted that consultations with clinical experts concluded that it would be unrealistic to restrict the use of Panhematin to this limited population. As such, CADTH reanalyses considering wider (and more probable, according to clinical experts consulted by CBS) patient populations are presented in the following section.

Seventy-six per cent of newly diagnosed patients with AIP reported in the Elder et al. (2013) study were women.[12] Assuming that the gender proportion of incident patients is consistent with the gender proportion of prevalent patients, and also assuming the prevalence of AIP in Canada is consistent with 0.54 per 100,000 as reported in Elder et al. (2013), and assumed in the manufacturer's model, 76% of these patients will be women; i.e., 0.41 per 100,000 people are women with AIP (0.54 multiplied by 76%). Additionally, a 2014 US study[9] reported that 30 of 63 (48%) female patients with AIP reported severe pre-menstrual symptoms; this estimate was assumed to represent the proportion of female patients with attacks temporally related to their menstrual cycle. According to the manufacturer's model, 5.3% of patients with AIP have recurrent attacks, while 20% have a sporadic attack per year; multiplying these estimates by the 48% of women with menstrual-related attacks yields 2.5% of patients having recurrent attacks, and 9.5% having sporadic attacks. As all of these estimates are based on limited source data and generalized to the indicated Canadian population through assumptions, alternate values for each parameter are explored in sensitivity analyses, reported in Table 8.

Of note, should the reimbursement of Panhematin be limited to its Health Canada indication, the number of patients estimated to be treated per year would *decrease* — in comparison to those who were treated through the Health Canada SAP in 2017 — from 18 to 17. Treating these patients would cost approximately $[redacted] in 2019, rising to $[redacted] by 2021. See Table 6.

Table 6: CADTH's Patient Numbers and Budget Impact Results When Population is Restricted to the Approved Indication

	Baseline 2018	Year 1 2019	Year 2 2020	Year 3 2021
Population of Canada, excluding Quebec, projected	28,557,550	28,803,145	29,050,852	29,300,689
Prevalent manifest AIP				
Number of prevalent female AIP patients (A)	117	118	119	120
Prevalent female AIP patients with recurrent attacks related to menstruation (A x 5.3% x 48%)	3	3	3	3
Prevalent female AIP patients with sporadic attack related to menstruation (A x 20% x 48%)	11	11	11	11
Incident symptomatic AIP patients				
Incident symptomatic female AIP patients	3	3	3	3
Incident symptomatic female AIP requiring hospitalization (and Panhematin, assumption)	2	2	2	2
Total number of treated patients	16	17	17	17
Total number of treated attacks	25	26	26	26
Number of Panhematin vials used				
For patients with recurrent attacks (4 attacks using 4 vials each)	47	48	48	49
For patients with sporadic attacks (1 attack using 4 vials)	45	45	45	46
For hospitalized incident patients (1 attack using 4 vials)	9	9	9	9
TOTAL vials per year estimate	**101**	**102**	**103**	**104**
Cost of treating AIP attacks				
Cost of prevalent patients with recurrent attacks	[redacted]	[redacted]	[redacted]	[redacted]
Cost of prevalent patients with sporadic attacks	[redacted]	[redacted]	[redacted]	[redacted]
Cost of hospitalized incident patients	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL predicted cost per year	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL predicted cost for first three years		**$2,609,279**		

AIP = acute intermittent porphyria.

Note: Calculated figures are rounded to the nearest whole patient or attack and may not precisely add up to the presented totals. The total estimated number of patients who may be treated with Panhematin includes prevalent patients with recurrent attacks, prevalent patients with sporadic attacks, and incident patients requiring hospitalization.

CADTH Analyses of Wider AIP Patient Populations Who May Receive Panhematin

The clinical experts consulted by CBS were of the opinion that Panhematin, if made available through CBS, would also be used for patients with recurrent AIP with attacks not related to their menstrual cycles. CADTH therefore conducted analyses assuming two alternate populations that could receive Panhematin treatment:

- women, regardless of temporal relation to menstrual cycle, with moderate-to-severe AIP attacks
- all patients, regardless of gender, with moderate-to-severe AIP attacks in.

As can be seen in Table 7, removing the requirement that the acute attack be temporally related to the menstrual cycle increased the estimated cost of Panhematin therapy in women to approximately $[redacted] million per year. If Panhematin is made available to all AIP patients with acute attacks, regardless of gender, then the estimated cost of Panhematin therapy

would increase to approximately $[redacted] million per year in the first three years, treating an estimated 41 patients.

This latter estimate relates to the population that the clinical experts consulted by CBS considered to be most likely to receive Panhematin in practice, and this estimate is similar to that of the manufacturer (see Table 2 and Table 3); however, CADTH's analysis appropriately accounted for the lower rate at which male AIP patients have been reported to suffer recurrent attacks (2.8% rather than 5.3%), and thus only seven patients are estimated as having recurrent attacks per year, rather than eight.

Table 7: Possible Patient Populations Based on CADTH Reanalysis

Eligible Population Scenario	Model Parameters	Patients Treated in Year 1	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
Restricted to indication; AIP attacks temporally related to menstrual cycle	Prevalence: • 0.54 per 100,000 manifest AIP • 76% female • 48% females related to menstruation • 5.3% of women have recurrent attacks	3 recurrent, 11 sporadic, 2 incident	[redacted]	[redacted]	[redacted]	2,609,279
AIP attacks in women	Removed 48% estimate of proportion of women with attacks related to menstrual cycle	6 recurrent, 24 sporadic, 2 incident	[redacted]	[redacted]	[redacted]	5,217,088
AIP attacks regardless of gender	• Removed 48% estimate of proportion of women with attacks related to menstrual cycle • Removed 76% estimate of women with AIP • Corrected proportion of patients having recurrent attacks from 5.3% of women to weighted average by gender (men's proportion = 2.8%, weighted average = 4.7%)	7 recurrent, 31 sporadic, 2 incident	[redacted]	[redacted]	[redacted]	6,405,508

AIP = acute intermittent porphyria.

Note: Calculated patients are presented rounded to the nearest whole number and may not precisely add up to the presented totals.

CADTH Sensitivity Analyses

A number of assumptions were made in both the manufacturer's analysis and CADTH's reanalysis. In order to explore uncertainty due to these assumptions, CADTH conducted a series of sensitivity analyses around several parameters, including the prevalence of AIP assumed in the Canadian population, the proportion of patients with recurrent attacks, the proportion of patients with sporadic attacks, the proportion of women with attacks temporally related to their menstrual cycles, the average duration of therapy per attack, the inclusion of estimated costs for infusion and lab tests associated with the administration of Panhematin, and the cost of reconstituting Panhematin with albumin rather than sterile water. Details of these changed parameters can be found in Table 5, while results for sensitivity analyses around CADTH reanalysis based on restricted indication can be seen in Table 8. Results

ranged from approximately $[redacted] per year, to about $[redacted] million per year, and were sensitive to assumptions which altered the number of patients treated, as well as those assumptions that changed the duration of treatment, and thus the number of Panhematin vials used per AIP attack. Sensitivity analyses incorporating other costs such as that of infusion administration and additional lab tests, or reconstituting Panhematin with albumin instead of sterile water, had minimal impact.

Table 8: Sensitivity Analyses Based on the CADTH Reanalysis Population Restricted to the Indication — Women With AIP Attacks Related to Their Menstrual Cycles

Analysis	Sensitivity Input[a]	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
CADTH base case	Reference, see Table 6	[redacted]	[redacted]	[redacted]	2,609,279
AIP prevalence low	Low 95% CI limit: 0.45 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	2,214,157
AIP prevalence high	High 95% CI limit: 0.63 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	3,004,402
AIP prevalence equal to that of Sweden	AIP prevalence 2.30 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	10,336,121
AIP prevalence equal to that of Switzerland	AIP prevalence 0.99 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	4,584,892
Fewer recurrent patients	Low 95% CI limit: 4% have recurrent attacks,[12] 48% menstrual-related[9]	[redacted]	[redacted]	[redacted]	2,310,060
More recurrent patients	High 95% CI limit: 6.9% have recurrent attacks,[12] 48% menstrual-related[9]	[redacted]	[redacted]	[redacted]	2,977,549
Fewer sporadic patients	15% of patients with manifest AIP have a sporadic attack per year (assumption)	[redacted]	[redacted]	[redacted]	2,321,569
More sporadic patients	25% of patients with manifest AIP have a sporadic attack per year (assumption)	[redacted]	[redacted]	[redacted]	2,896,990
Low proportion related to menstruation	25% of women with manifest AIP have attacks temporally related to menstrual cycle (assumption)	[redacted]	[redacted]	[redacted]	1,483,180
High proportion related to menstruation	75% of women with manifest AIP have attacks temporally related to menstrual cycle (assumption)	[redacted]	[redacted]	[redacted]	3,310,718
Minimum treatment length	AIP attacks associated with the recommended minimum duration of treatment (3 days)[1]	[redacted]	[redacted]	[redacted]	1,956,960
Longer average treatment	AIP attacks associated with 6 days of treatment rather than 4 as in base case (assumption)	[redacted]	[redacted]	[redacted]	3,913,919
Maximum treatment length	AIP attacks associated with the recommended maximum duration of treatment (14 days)[1]	[redacted]	[redacted]	[redacted]	9,132,478

Analysis	Sensitivity Input[a]	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
Cost, including infusion and lab tests	Daily cost of infusion and lab tests associated with Panhematin treatment estimated using: G381 — Infusion of standard chemo or biologic with minor toxicity ($54.25)[14] L199 — Delta-aminolevulinic acid, quantitative urine ($12.93)[15] L198 — Porphobilinogen, quantitative urine ($12.93)[15] L201— Porphyrins, quantitation (coproporphyrin, protoporphyrin, uroporphyrin) urine ($31.02)[15]	[redacted]	[redacted]	[redacted]	2,617,866
Cost, including reconstitution with albumin	Each vial of Panhematin is reconstituted with 132 mL of 25% human serum albumin, using three 50 mL vials ([redacted] per vial, excess wasted)[6]	[redacted]	[redacted]	[redacted]	2,633,137

AIP = acute intermittent porphyria; 95% CI = 95% confidence interval.
[a] More information on the rationale behind the chosen sensitivity parameters can be found in Table 5..

Sensitivity analyses were also conducted around the scenarios which include wider populations of AIP patients. Those conducted based on all female AIP patients requiring treatment (i.e., access not limited to attacks linked to menstrual cycles) can be found in Table 9 (range: approximately $[redacted] million to $[redacted] million per year), while sensitivity analyses using all AIP patients requiring treatment, regardless of gender, can be found in Table 10 (range: approximately $[redacted] million to $[redacted] million per year).

Table 9: Sensitivity Analyses Based on the CADTH Reanalyses Population — Women With AIP Attacks, Regardless of Relation to Menstrual Cycle

Analysis	Sensitivity Input	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
CADTH scenario with base assumptions	Reference, see Table 7	[redacted]	[redacted]	[redacted]	5,217,088
AIP prevalence low CI	Low 95% CI limit: 0.45 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	4,387,331
AIP prevalence high CI	High 95% CI limit: 0.63 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	6,046,846
AIP prevalence equal to that of Sweden	AIP prevalence 2.30 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	21,443,455
AIP prevalence equal to that of Switzerland	AIP prevalence 0.99 per 100,000, 76% female[12]	[redacted]	[redacted]	[redacted]	9,365,875
Fewer recurrent patients	Low 95% CI limit: 4% have recurrent attacks[12]	[redacted]	[redacted]	[redacted]	4,588,728
More recurrent patients	High 95% CI limit: 6.9% have recurrent attacks[12]	[redacted]	[redacted]	[redacted]	5,990,454

Analysis	Sensitivity Input	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
Fewer sporadic patients	15% of patients with manifest AIP have a sporadic attack per year (assumption)	[redacted]	[redacted]	[redacted]	4,612,896
More sporadic patients	25% of patients with manifest AIP have a sporadic attack per year (assumption)	[redacted]	[redacted]	[redacted]	5,821,281
Minimum treatment length	AIP attacks associated with the recommended minimum duration of treatment (3 days)[1]	[redacted]	[redacted]	[redacted]	3,912,816
Longer average treatment	AIP attacks associated with 6 days of treatment rather than 4, as in base case (assumption)	[redacted]	[redacted]	[redacted]	7,825,633
Maximum treatment length	AIP attacks associated with the recommended maximum duration of treatment (14 days)[1]	[redacted]	[redacted]	[redacted]	18,259,809
Cost, including infusion and lab tests	Daily cost of infusion and lab tests associated with Panhematin treatment estimated using: G381 — Infusion of standard chemo or biologic with minor toxicity ($54.25)[14] L199 — Delta-aminolevulinic acid, quantitative urine ($12.93)[15] L198 — Porphobilinogen, quantitative urine ($12.93)[15] L201— Porphyrins, quantitation (coproporphyrin, protoporphyrin, uroporphyrin) urine ($31.02)[15]	[redacted]	[redacted]	[redacted]	5,285,764
Cost, including reconstitution with albumin	Each vial of Panhematin is reconstituted with 132 mL of 25% human serum albumin, using three 50 mL vials ([redacted] per vial, excess wasted)[6]	[redacted]	[redacted]	[redacted]	5,264,790

AIP = acute intermittent porphyria; 95% CI = 95% confidence interval.

Table 10: Sensitivity Analyses Based on the CADTH Reanalysis Population — Patients With AIP Attacks, Regardless of Gender

Analysis	Sensitivity Input	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
CADTH base case	Reference, see Table 7	[redacted]	[redacted]	[redacted]	6,405,508
AIP prevalence low	Low 95% CI limit: 0.45 per 100,000[12]	[redacted]	[redacted]	[redacted]	5,377,681
AIP prevalence high	High 95% CI limit: 0.63 per 100,000[12]	[redacted]	[redacted]	[redacted]	7,433,336
AIP prevalence equal to that of Sweden	AIP prevalence 2.30 per 100,000[12]	[redacted]	[redacted]	[redacted]	26,505,243

Analysis	Sensitivity Input	Year 1 2019 ($)	Year 2 2020 ($)	Year 3 2021 ($)	3-Year Total ($)
AIP prevalence equal to that of Switzerland	AIP prevalence 0.99 per 100,000[12]	[redacted]	[redacted]	[redacted]	11,544,645
Fewer recurrent patients	Low 95% CI limit: • 4% of women have recurrent attacks • 1.4% of men do • weighted by gender[12]	[redacted]	[redacted]	[redacted]	5,563,842
More recurrent patients	High 95% CI limit: • 6.9% of women have recurrent attacks • 5.4% of men do • weighted by gender[12]	[redacted]	[redacted]	[redacted]	7,575,014
Fewer sporadic patients	15% of patients with manifest AIP have a sporadic attack per year (assumption)	[redacted]	[redacted]	[redacted]	5,610,864
More sporadic patients	25% of patients with manifest AIP have a sporadic attack per year (assumption)	[redacted]	[redacted]	[redacted]	7,200,152
Minimum treatment length	AIP attacks associated with the recommended minimum duration of treatment (3 days)[1]	[redacted]	[redacted]	[redacted]	4,804,131
Longer average treatment	AIP attacks associated with 6 days of treatment rather than 4, as in base case (assumption)	[redacted]	[redacted]	[redacted]	9,608,262
Maximum treatment length	AIP attacks associated with the recommended maximum duration of treatment (14 days)[1]	[redacted]	[redacted]	[redacted]	22,419,279
Cost, including infusion and lab tests	Daily cost of infusion and lab tests associated with Panhematin treatment estimated using: G381 — Infusion of standard chemo or biologic with minor toxicity ($54.25)[14] L199 — Delta-aminolevulinic acid, quantitative urine ($12.93)[15] L198 — Porphobilinogen, quantitative urine ($12.93)[15] L201 — Porphyrins, quantitation (coproporphyrin, protoporphyrin, uroporphyrin) urine ($31.02)[15]	[redacted]	[redacted]	[redacted]	6,489,827
Cost, including reconstitution with albumin	Each vial of Panhematin is reconstituted with 132 mL of 25% human serum albumin, using three 50 mL vials ([redacted] per vial, excess wasted)[6]	[redacted]	[redacted]	[redacted]	6,464,076

AIP = acute intermittent porphyria; 95% CI = 95% confidence interval.

In addition, it is noted that the prophylactic use of hemin therapy has been described in the literature[8,16] as well as in guidelines,[3] although such use has not been approved by regulatory agencies. The majority of patients who have been treated prophylactically in these studies received an infusion of hemin either weekly or biweekly, through a central line. Based on this, the cost of prophylactic Panhematin therapy in Canada, should the option be available, would be approximately [redacted] (assuming biweekly infusions) to [redacted] (assuming weekly infusions) per patient, per year. However, it is not known what proportion of recurrent patients might receive Panhematin prophylactically.

Jurisdictional Budget Impact

The manufacturer's model attempted to estimate the proportion of Panhematin costs that would be borne within each province and territory, excluding Quebec, by multiplying the total projected budget by the proportion of the national population residing within each jurisdiction. Budget impact for the three AIP groups modelled by CADTH can be found in Table 11. This analysis assumes that the prevalence of AIP is the same across jurisdictions in Canada, as actual differences in the prevalence of porphyria among jurisdictions is unknown. In addition, this analysis cannot provide estimates of the proportion of the costs that would be borne specifically by Federal health care programs, rather than provinces or territories. Finally, these estimates only reflect the cost of Panhematin vials and do not represent the full implementation cost of providing access to Panhematin.

Table 11: CADTH's Estimated Budget Impact of Reimbursing Panhematin by Jurisdiction in Three Population Scenarios

Jurisdiction	Estimated Population 2018	Proportion of National Population	Cost if Population Restricted to Women With AIP Attacks Related to Menstrual Cycle ($)			Cost if Population Restricted to Women With AIP Attacks ($)			Cost if Population Restricted to Patients With AIP attacks, Regardless of Gender ($)		
			Year 1 2019	Year 2 2020	Year 3 2021	Year 1 2019	Year 2 2020	Year 3 2021	Year 1 2019	Year 2 2020	Year 3 2021
Canada, excluding Quebec	28,557,550	100.00%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Newfoundland and Labrador	533,365	1.87%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prince Edward Island	153,328	0.54%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nova Scotia	962,072	3.37%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New Brunswick	766,188	2.68%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ontario	14,315,447	50.13%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Manitoba	1,349,617	4.73%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Saskatchewan	1,173,935	4.11%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alberta	4,322,995	15.14%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
British Columbia	4,858,588	17.01%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yukon	38,790	0.14%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Northwest Territories	44,903	0.16%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nunavut	38,323	0.13%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIP = acute intermittent porphyria.

Note: National population excludes that of Quebec.

Conclusion

The manufacturer submitted a price of [redacted] per 268 mg vial of Panhematin. Based on the manufacturer's budget impact analysis, and assuming coverage is limited only to the indicated population — i.e., women with AIP attacks temporally related to their menstrual cycles — CADTH's analysis suggests the funding of Panhematin would cost approximately [redacted] in the first year, rising to [redacted] by year 3.

This estimate is, however, inconsistent with the views of the clinical experts consulted by CBS suggesting, that it would be unrealistic, in clinical practice, to restrict the use of Panhematin to its indicated population. When considering a population of all patients with AIP attacks requiring treatment, regardless of gender, CADTH's estimate increased to 41 patients being treated each year for the first three years, at a cost of approximately $[redacted] million [redacted].

There are substantial uncertainties associated with the analysis given the lack of information about patients likely to access treatment. A series of sensitivity analyses were run on each population of AIP patients modelled to test each assumption, leading to a range of estimates between $[redacted] to almost $[redacted] million per year. The potential for Panhematin to be used in even broader populations exists but could not be formally assessed. Additionally, this analysis does not consider the potential benefits associated with Panhematin treatment, merely the additional cost of therapy.

References

1. Panhematin: hemin for injection 268 mg hemin per vial sterile powder for reconstitution for injection [product monograph]. Toronto (ON): Recordati Rare Diseases Canada Inc.; 2018 Jul 13: https://pdf.hres.ca/dpd_pm/00046317.PDF. Accessed 2018 Oct 3.
2. Recordati Rare Diseases Canada Inc. Panhematin Budget Impact Model 2018 - national final. Toronto (ON): Recordati Rare Diseases Canada, Inc.; 2018.
3. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. *Br J Haematol.* 2017;176(4):527-538.
4. Ramanujam VM, Anderson KE. Porphyria diagnostics-Part 1: a brief overview of the porphyrias. *Curr Protoc Hum Genet.* 2015;86:17.20.11-26.
5. Canadian Association for Porphyria. Patient survey - access to heme treatment in Canada, 2016. Edmonton (AB): Canadian Association for Porphyria; 2016.
6. Anderson KE, Bonkovsky HL, Bloomer JR, Shedlofsky SI. Reconstitution of hematin for intravenous infusion. *Ann Intern Med.* 2006;144(7):537-538.
7. Herrick AL, McColl KE, Moore MR, Cook A, Goldberg A. Controlled trial of haem arginate in acute hepatic porphyria. *Lancet.* 1989;1(8650):1295-1297.
8. Anderson KE, Collins S. Open-label study of hemin for acute porphyria: clinical practice implications. *Am J Med.* 2006;119(9):801 e819-824.
9. Bonkovsky HL, Maddukuri VC, Yazici C, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. *Am J Med.* 2014;127(12):1233-1241.
10. Stein P, Badminton M, Barth J, et al. Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Ann Clin Biochem.* 2013;50(Pt 3):217-223.
11. Canadian Blood Services. Medical and scientific review report of Panhematin® for the Canadian Agency for Drugs and Technologies in Health (CADTH). Ottawa (ON): Canadian Blood Services; 2018.
12. Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. *J Inherit Metab Dis.* 2013;36(5):849-857.
13. Normosang 25 mg/ml, concentrate for solution for infusion - summary of product characteristics, labelling and package leaflet. Puteaux (FR): Orphan Europe; 2015: http://www.orphan-europe.com/files/files/SMPC/20151104_NORMOSANG_PRODUCT_INFORMATION.pdf. Accessed 2018 Oct 18.
14. Ontario Ministry of Health and Long Term Care. Schedule of Benefits: Physician Services under the Health Insurance Act (October 30, 2015 (effective December 21, 2015)). Toronto (ON): Ontario Ministry of Health and Long Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20151221.pdf. Accessed 2018 Oct 3.
15. Ontario Ministry of Health and Long Term Care. Schedule of Benefits for Laboratory Services. Toronto (ON): Ontario Ministry of Long Term Care; 2017: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn.pdf. Accessed 2018 Oct 3.
16. Marsden JT, Guppy S, Stein P, et al. Audit of the use of regular haem arginate infusions in patients with acute porphyria to prevent recurrent symptoms. *JIMD Rep.* 2015;22:57-65.