Canadian Journal of Health Technologies

CADTH

September 2021 Volume 1 Issue 9

CADTH Reimbursement Recommendation

Givosiran (Givlaari)

Indication: For the treatment of acute hepatic porphyria (AHP) in adults

Sponsor: Alnylam Netherlands B.V.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Givlaari?

CADTH recommends that Givlaari should be reimbursed by public drug plans for the treatment of acute hepatic porphyria (AHP) in adults if certain conditions are met.

Which Patients Are Eligible for Coverage?

Givlaari should only be covered to treat patients who have experienced 4 or more attacks requiring either hospitalization, an urgent health care visit, or intravenous hemin in the year prior to the prescribing date.

What Are the Conditions for Reimbursement?

Givlaari should only be reimbursed if prescribed by a clinician experienced in the management of AHP, if it is not used in combination with prophylactic hemin, and if the cost of Givlaari is reduced. Reimbursement of Givlaari should be renewed after 12 months if there is a reduction in the annualized attack rate.

Why Did CADTH Make This Recommendation?

- Evidence from 1 randomized clinical trial demonstrated that Givlaari resulted in a decrease in the annualized porphyria attack rate compared with placebo.
- Givlaari meets some of the needs identified by patients, such as preventing attacks, but does not appear to reduce symptoms of AHP.
- Using the sponsor-submitted price, Givlaari is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to best supportive care. Therefore, a price reduction is required. Economic evidence suggests that a price reduction of at least 57% is needed to ensure Givlaari is cost-effective at a $50,000 per QALY threshold.
- The 3-year budget impact is $181 million.

Additional Information

What Is AHP?

AHP is a family of rare genetic disorders that cause altered enzyme activity in the liver, which ultimately leads to acute porphyria attacks. Attacks are associated with a gradual increase in significant pain that can last for several days. Long-term complications of recurrent acute attacks may include chronic pain, chronic kidney failure, and liver damage. The estimated prevalence of AHP in Canada (excluding Quebec) is 15.13 per million population.

Unmet Needs in AHP

In the absence of a cure, there is a need for a treatment that prevents attacks and reduces symptoms, particularly pain, nerve damage, and paralysis.

How Much Does Givlaari Cost?

Treatment with Givlaari is expected to cost approximately $773,448 per patient per year, assuming patient weight is less than 75.7 kg.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that givosiran should be reimbursed for the treatment of acute hepatic porphyria (AHP) in adults only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Study 003 (ENVISION) evaluated the efficacy and safety of givosiran administered once monthly in patients with AHP who were at least 12 years old. Patients enrolled in the study had a documented diagnosis of acute intermittent porphyria (AIP), coproporphyria, or variegate porphyria and had recurrent attacks requiring hospitalization, an urgent health care visit, or IV administration of hemin at home. In patients with AIP, treatment with givosiran resulted in a 74% reduction in the annualized porphyria attack rate relative to patients who received placebo (rate ratio = 0.26; 95% confidence interval [CI], 0.16 to 0.41; P < 0.001). Patients identified a need for a treatment that prevents attacks and reduces symptoms. The primary outcome result from the trial suggests that givosiran may meet some of these needs.

Using the sponsor-submitted price for givosiran, the incremental cost-effectiveness ratio (ICER) for givosiran in patients with AHP with recurrent attacks was $14,211,820 per quality-adjusted life-year (QALY) compared with best supportive care (BSC). At this ICER, givosiran is not cost-effective at a $50,000 per QALY willingness to pay threshold for adults with AHP experiencing recurrent attacks. A reduction in price of at least 57% is required for givosiran to be considered cost-effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Reimbursement of givosiran should be restricted to patients with 4 or more attacks requiring either hospitalization, an urgent health care visit, or IV hemin in the year before the prescribing date.	• The ENVISION study demonstrated statistically significant benefit of givosiran over placebo in patients who had 2 or more porphyria attacks requiring either hospitalization, an urgent health care visit, or treatment with IV hemin at home within the 6 months before screening. • An annual rate is consistent with established clinical guidelines and may reflect the variability of the disease. One year also allows a more stable estimate of baseline for assessing response to treatment.
Renewal	
2. A reduction in the annualized attack rate after 12 months of therapy compared to baseline.	• An annual rate is consistent with established clinical guidelines and may reflect the variability of the disease.

Reimbursement condition	Reason
Prescribing	
3. Prescription should be restricted to a clinician experienced in the management of AHP. 4. Should not be used in combination with prophylactic hemin.	• Accurate diagnosis of patients with AHP is important to ensure that givosiran is prescribed to appropriate patients. • There is no evidence to support efficacy and safety of combining givosiran with prophylactic hemin therapy. Clinical experts' input also indicated that such a combination for prophylaxis is not supported by evidence or by clinical experience.
Pricing	
5. A reduction in price.	• The ICER for givosiran, in a subgroup of patients with AHP who have recurrent attacks, is $14,211,820 compared BSC. A price reduction of 57% would be required for givosiran to be able to achieve an ICER of $50,000 per QALY compared with BSC.

AHP = acute hepatic porphyria; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Implementation Guidance

1. "Urgent health care visit" should be defined in the context of each jurisdiction. In the pivotal trial, ENVISION, urgent health care visit was defined as an urgent, unscheduled office or practice, infusion centre, or an emergency department visit that did not meet the criteria for a hospitalization (at least 24 hours stay in an inpatient or emergency unit).
2. With givosiran supplied in single-use vials, patients weighing more than 75.6 kg may need 2 vials each month, which would have a considerable impact on the estimated cost-effectiveness of givosiran. CDEC recommends that drug plans implement cost-containment policies to mitigate potential drug wastage, such as a cap on the cost of each administration based on the cost of a single vial, which reflects assumptions in the submitted pharmacoeconomic model.
3. Although CDEC noted that givosiran should not be used in combination with prophylactic hemin, this does not exclude the use of hemin for the treatment of acute attacks in givosiran-treated patients.
4. CADTH reanalysis estimated that, at the submitted price, the potential incremental budget impact of reimbursing givosiran is approximately $60 million per year, which the Committee considered to be a substantial barrier to implementation.

Discussion Points

- Considering the potential of givosiran to be a life-long therapy, CDEC noted that the comparative efficacy and safety of givosiran is limited to the 6-month duration of ENVISION. Although data related to efficacy and safety up to 36 months exist in the form of open-label, non-comparative, extension studies, the evidence is limited in quantity and quality.

- CDEC noted that AHP can have variable presentations and a fluctuating course, and challenges exist in clinical diagnosis and management of patients with AHP. The Committee determined that assessment of attacks over the course of the year could provide accommodation to the variable nature of the disease. AHP is rare disease and only a proportion of patients diagnosed with AHP will experience recurrent attacks.
- CDEC noted that in the patient group submission, patients noted experiencing the following symptoms: pain, fatigue, nausea, weakness, paralysis, neuropathy, seizures, anxiety, and depression, among others. Patients expressed the desire for a treatment that prevents attacks and reduces symptoms, particularly pain, nerve damage, and paralysis, and restores quality of life. In ENVISION, health-related quality of life (HRQoL) was evaluated using the 12-item Short-Form Health Survey (SF-12), EuroQol 5-dimension 5-level (EQ-5D-5L), and Patient Global Impression of Change (PGIC). However, none of these measures have been validated in this patient population, and all related results were not adjusted for multiple testing. Other symptom-related outcomes, including pain, fatigue, and nausea, either did not show a statistically significant result or were outside of the statistical testing hierarchy and not adjusted for multiple testing. As such, no conclusion could have been made on the effect of givosiran on these outcomes. There is no conclusive evidence to support any effect of givosiran on chronic neurologic or psychiatric complications of AHP.
- Although prophylactic hemin and GnRH analogues are used in the management of AHP, they are associated with toxicities, complications, and contraindications that limit long-term usefulness; prescribing decisions likely need to be individualized. Clinical experts suggested that some patients may be managed through avoidance of precipitating factors and the occasional use of IV glucose and/or hemin therapy given during acute attacks.

Background

Givosiran has a Health Canada indication for AHP in adults. Givosiran is a double-stranded small interfering RNA. It is available as a solution for subcutaneous injection (189 mg/mL) and the Health Canada–approved dose is 2.5 mg/kg once monthly, based on body weight.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of 1 pivotal multi-centre, placebo-controlled, double-blind, phase III study clinical trial in adults with AHP
- a summary of a phase I clinical trial and a phase I/II clinical trial in adult patients with AHP
- patient perspectives gathered by 2 patient groups: the Canadian Association for Porphyria/ Association Canadienne de Porphyrie (CAP) and American Porphyria Foundation (APF)
- three clinical specialists with expertise diagnosing and treating patients with AHP
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to the call from CADTH for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

CADTH received 2 patient group submissions for this review from CAP and APF. CAP is a national, voluntary charity whose mission is to deliver evidence-based information and support to patients with porphyria, their families, health care providers, and the general public. APF provides programs to raise awareness and educate health care professionals and the general public in 76 countries around the world. Of its international members, more than 300 are from Canada. To obtain input for this review, CAP distributed a survey to its members in February 2021, which was restricted to Canadian patients and caregivers with experience with AHP. In total, 22 patients and 4 caregivers responded to the survey. CAP also requested support from the British Porphyria Association, which shared 3 interviews from individuals who had received givosiran. APF used their social media platforms and entertainment news to connect with Canadian patients about their experiences with porphyria, and responses were collected by telephone and email. Some of the responses in the APF submission were collected during an Alnylam Patient Advisory Board meeting. Twelve individual patient submissions were collected from Canadians.

Respondents in both submissions noted experiencing the following symptoms: pain, fatigue, nausea, weakness, paralysis, neuropathy, seizures, anxiety, and depression, among others. More than 80% of patients from the CAP survey had experienced symptoms at least once a month, with many reporting these symptoms occurring more than 20 days per month. The group also reported that 86% of respondents had at least 1 attack in the past year and 36% had at least 10. Furthermore, 55% of patients had gone to the emergency department at least once in the past year due to an attack while 18% had gone at least 10 times. Porphyria attacks can also prevent patients and caregivers from being able to work, lead to poorer quality of life, and negatively impact relationships. The patient input submissions described how symptoms and attempting to avoid triggers could strain social relationships and make it difficult to care for their families. Both groups emphasized the negative effect that porphyria had on daily life and mental health.

Respondents ideally would like a cure for porphyria, although they also believe a realistic short-term goal is to have a treatment that prevents attacks and reduces symptoms, particularly pain, nerve damage, and paralysis. Patients and caregivers would like to see additional options that are more effective, have fewer side effects, have an easier mode of administration, can be administered outside of a hospital, and lead to improvements in quality of life. Other limitations to accessing treatments that were identified include the need for travel, requirement for venous access, and lack of access to specialists and proper diagnostic testing.

Clinician Input

Input From Clinical Experts Consulted by CADTH

One of the major goals in the management of AHP is to reduce the frequency of AHP attacks. According to the clinical experts consulted for this review, most patients with recurrent

attacks will continue to have recurrent attacks with currently available treatment strategies. The experts noted that although prophylactic hemin can be used to reduce the rate of AHP attacks with case reports of improvement, use of prophylactic hemin is outside of the Health Canada–approved indication and has not been studied well. GnRH may also be used to prevent AHP attacks, but it is not approved for prolonged use and is associated with climacteric symptoms and loss of bone mineral density.

As per feedback from the clinical experts for this review, givosiran would be used in patients who have recurrent attacks because there is no evidence to support its use in asymptomatic individuals or in treating acute attacks. The clinical experts felt that givosiran would not be used as a first-line treatment or to treat the first AHP attack, and recommended that other approaches to treatment, such as avoidance of triggers, should be tried for patients with AHP before givosiran. The experts expected givosiran to provide an alternative therapy for a small subset of patients with frequent or recurrent attacks who would otherwise require frequent hospitalization and hemin administration. The experts recommended that givosiran is reserved for patients with recurrent symptoms or flares that are consistently affecting HRQoL. Givosiran was also described by the experts as an appropriate treatment for patients that qualify for hemin prophylaxis but cannot adhere to treatment due to toxicity or lack of convenience.

The following outcomes were noted by the clinical experts as those that are used to determine response to treatment in clinical practice: reduced attack rate, reduced hospitalization, reduced need for hemin, frequency of neurovisceral flares, and improved patient-reported outcomes, such as daily symptoms, HRQoL, and work-life productivity. The clinical experts indicated that patients are assessed for response to treatment every 6 months or annually. All the experts agreed that 1 year would be a sufficient amount of time to assess a patient's response to treatment; however, the variable presentation of the disease, such as yearly fluctuations in attack frequency, was noted as a limitation in this assessment.

In general, the clinical experts felt that patients treated with givosiran would continue with treatment until there is a reason for discontinuation, such as safety concerns or an increase or a similar rate of attacks with treatment, which may indicate that treatment might not be working. The clinical experts also indicated that menopause would be a potential reason to trial treatment discontinuation in patients with stable disease. However, it was challenging for the clinicians to specifically define "response to treatment" due to the heterogenous nature of AHP among patients. The clinical experts also noted that if attacks recurred following discontinuation, restarting treatment with givosiran would be a possibility.

Clinician Group Input

CADTH did not receive any input from clinician groups for this review.

Drug Program Input

The drug programs inquired about requirements for diagnosis of types of AHP, the use of givosiran outside of the criteria used in ENVISION , discontinuation of therapy, concern for use of givosiran in combination with hemin for an acute attack, and generalizability issues for non-AIP types of AHP. The clinical experts noted that the biochemical tests for urinary delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) are specific to AHP and, along with clinical evidence consistent with porphyria attacks, are sufficient to make a diagnosis; genetic tests are not required. The clinical experts indicated that treatment decisions would be made on a case-by-case basis using clinical judgment but would generally be guided by the

criteria outlined in the pivotal trial. The clinical experts did not express concern with the use of givosiran in combination with hemin, and the results of the trial in patients with AIP were considered generalizable to all patients with AHP.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One multi-centre, placebo-controlled, double-blind, phase III study was included in the CADTH systematic review, ENVISION. ENVISION was designed to evaluate the efficacy and safety of givosiran administered once monthly in patients with AHP. Included patients had to be at least 12 years old with a documented diagnosis of AIP, coproporphyria, variegate porphyria, or ADP; have at least 2 composite porphyria attacks within 6 months before screening; and be willing to abstain from prophylactic use of hemin during the trial. The primary objective was to evaluate the effect of subcutaneous givosiran compared with placebo in the rate of porphyria attacks requiring hospitalization, an urgent health care visit, or IV hemin administration at home over 6 months in patients with AIP. The annualized rate of porphyria attacks in patients with AHP and the following assessments in patients with AIP were included as secondary outcomes: urinary ALA and PBG levels; hemin use; daily worst scores for symptoms including pain, fatigue, and nausea; and HRQoL via the SF-12. Opioid use, the Porphyria Patient Experience Questionnaire (PPEQ), and ability to work or attend school, as well as the secondary end points analyzed in patients with AHP, were included as exploratory outcomes. ENVISION implemented a statistical hierarchy to control for multiple testing, in which the first outcome to be tested was the annualized attack rate (AAR) in patients with AIP over the 6-month double-blind period followed by the following outcomes (conducted in patients with AIP unless indicated otherwise): urinary ALA levels at 3 months; urinary ALA levels at 6 months; urinary PBG levels at 6 months; annualized rate of administered hemin doses over the 6-month double-blind period; AAR in patients with AHP over the 6-month double-blind period; daily worst pain score, fatigue score, and nausea score over the 6-month double-blind period; and change from baseline in the Physical Component Summary (PCS) of the SF-12 at 6 months.

A total of 94 patients were randomized in ENVISION: 89 (95%) had AIP, 1 had coproporphyria, 2 had variegate porphyria, and 2 did not have an identified mutation. Patients with AIP were between the age of 19 and 65 years (mean age range = 37.3 to 40.7 years), 89% to 91% were female, and 35% to 40% resided in North America. Between 40% and 44% of patients had prior experience with the use of prophylactic hemin and, based on the composite definition of porphyria attacks, the median historical AAR was 8 attacks in both treatment groups (range = 0 to 46). Although not having a porphyria attack, between 48% and 56% of patients reported having chronic symptoms, and 28% to 30% of patients reported chronic opioid use. Baseline characteristics in patients with AHP were similar to those reported for patients with AIP.

Efficacy Results

The description of results provided here will focus on analyses conducted in the modified full analysis set for patients with AIP. Results based on the full analysis set in patients with all

types of AHP will only be described if there is a notable difference from the results based on the modified full analysis set.

The primary end point of the pivotal trial was the annualized rate of porphyria attacks in patients with AIP over the 6-month double-blind period, for which porphyria attacks were defined as events requiring hospitalization, an urgent health care visit, or IV hemin administration at home. The mean AAR based on the composite end point was 3.22 (95% CI, 2.25 to 4.59) and 12.52 (95% CI, 9.35 to 16.76) for patients in the givosiran treatment group and placebo treatment group, respectively. This corresponded to a 74% reduction in the rate of porphyria attacks for patients in the givosiran treatment group relative to patients receiving placebo (rate ratio = 0.26; 95% CI, 0.16 to 0.41; P < 0.001). The number of attacks for each of the components of the primary outcome were also reported. Treatment with givosiran corresponded to a 49% rate reduction in attacks that required hospitalization (rate ratio = 0.51; 95% CI, 0.25 to 1.04) and an 84% rate reduction in attacks requiring an urgent health care visit (ratio = 0.16; 95% CI, 0.09 to 0.31). A total of 3 attacks required IV hemin administration at home for patients in the givosiran treatment group compared with 32 for patients in the placebo treatment group (rate ratio was not assessed because n < 10 in the givosiran treatment group).

Health-related quality of life was evaluated using the SF-12, EQ-5D-5L, and PGIC. Each of these HRQoL outcomes is widely used in clinical trials; however, evidence of validity, reliability, and responsiveness, or a minimally important difference, in patients with AHP were not identified. All the HRQoL outcomes were reported as exploratory outcomes except for the PCS of the SF-12, which was a secondary outcome in ENVISION. At month 6, the least squares (LS) mean change from baseline in the PCS score was 5.37 (standard error of the mean [SEM] = 1.17) for the givosiran treatment group and 1.43 (SEM = 1.22) for the placebo treatment group. The between-group difference in the LS mean PCS score for givosiran compared with placebo was 3.94 (95% CI, 0.59 to 7.29; P = 0.0216). Due to a failure higher in the statistical testing hierarchy, the reported P value cannot be interpreted as statistically significant. The results of the change from baseline in the domain scores for the SF-12 suggest that the PCS score was driven by the "bodily pain" and "role physical" domains. The Mental Component Summary score of the SF-12 was reported descriptively. At month 6, the mean change from baseline in the Mental Component Summary score was 3.55 (standard deviation [SD] = 10.08) and 1.30 (SD = 8.54) for patients receiving givosiran and placebo, respectively. For the EQ-5D-5L index, the LS mean change from baseline at month 6 was [redacted] and [redacted] for the givosiran and placebo treatment groups, respectively. For the EQ-5D-5L visual analogue scale, the LS mean change from baseline at month 6 was [redacted] and [redacted] for the givosiran and placebo treatment groups, respectively. At month 6, the percentage of patients who reported their status improved from study start via the PGIC was 88.9% and 37.1% among patients in the givosiran and placebo treatment groups, respectively.

In terms of management of symptoms related to porphyria, the change in self-reported assessments of pain, fatigue, and nausea based on a numeric rating scale were reported in ENVISION. Post hoc non-parametric tests were used to evaluate daily worst pain following demonstration of a deviation from normality and failed statistical test using the analysis of covariance (ANCOVA) model. The median of the area under the curve for the change from baseline in the weekly mean score for daily worst pain over the 6-month treatment period was −11.5 (Q1, Q3: −29.2, 3.0) and 5.3 (Q1, Q3: −23.1 to 11.2) for the givosiran and placebo treatment groups, respectively. The treatment group difference for rating of daily worst pain was −10.1 (95% CI, −22.8 to 0.9; P = 0.0455) for givosiran compared with placebo. At

month 6, the changes from baseline in daily worst fatigue and daily worst nausea were also evaluated; a difference between treatment groups was not observed.

In ENVISION, hemin was only permitted as a rescue medication for the treatment of acute porphyria attacks and was reported as days of hemin use. In patients with AIP, 54% in the givosiran treatment group and 23% in the placebo treatment group reported zero days of hemin use over the 6-month treatment period. When compared with placebo, treatment with givosiran corresponded to a 77% rate reduction in days of hemin use based on a rate ratio of 0.23 (95% CI, 0.11 to 0.45; P < 0.001). Reported hemin use is consistent with the reduction in AAR reported for the primary outcome. The results for urinary levels of ALA and PBG were also consistent with the primary outcome. At month 6, urinary levels of ALA and PBG were lower among patients receiving givosiran than placebo. This corresponded to a between-group difference of −19.14 mmol/mol creatinine (Cr) (95% CI, −26.04 to −12.24; P < 0.001) for ALA levels and −36.20 mmol/mol Cr (95% CI, − 49.71 to − 22.70; P < 0.001) for urinary PBG levels, both in favour of givosiran.

Opioid use, the PPEQ, and days of missed work or school were also reported as exploratory efficacy outcomes in ENVISION. Reduced complications of AHP, hospitalization and health care use, and mortality were included in the systematic review protocol but were not reported in the pivotal trial. However, attacks requiring hospitalization and health care use were incorporated in the composite definition of acute porphyria attacks, and mortality was reported as a safety outcome.

The primary and key secondary outcomes, AAR and change in urinary ALA levels, were analyzed by subgroups. The only subgroup analysis of interest to this review was by high or low historical AAR. The subgroup analyses were consistent with the results in the overall population. Additionally, a number of sensitivity analyses were conducted to account for variation in the primary end point based on reporting of porphyria attacks, which were all consistent with the primary analysis.

Harms Results

In ENVISION, 85% of patients with AIP experienced at least 1 adverse event (AE), with nausea, injection site reaction, chronic kidney disease, fatigue, increase in ALT, and decrease in glomerular filtration rate more commonly reported among patients who received givosiran. Serious adverse events (SAEs) were reported more frequently among patients in the givosiran treatment group (17%) than in patients in the placebo treatment group (9%). Specific SAEs were infrequent, with the only SAEs reported by more than 1 person being chronic kidney disease (2 patients in the givosiran treatment group, 0 receiving placebo) and device-related infection (2 patients in the placebo treatment group, 1 receiving givosiran). A single patient randomized to receive givosiran withdrew from treatment due to an AE. The patient [redacted] discontinued treatment due to ALT elevation. No deaths were reported during the 6-month double-blind period of ENVISION.

Motor neuropathy, hepatocellular carcinoma, injection site reactions, transaminase elevation, and progression of renal impairment were included in the CADTH systematic review protocol as notable harms. As previously described, injection site reactions and transaminase elevation were more common among patients receiving givosiran. Nerve compression and peripheral neuropathy were reported for motor neuropathy and were more common in the placebo treatment group. There were no cases of hepatocellular carcinoma reported during

the 6-month treatment period, which may not have been a sufficient amount of time to observe this safety outcome.

Critical Appraisal

One of the limitations of the internal validity of the study was the lack of a specific minimally important difference for the composite primary outcome (AAR). The AAR was based on attacks requiring hospitalization, an urgent health care visit, or IV hemin administration at home. The clinical experts indicated that, in general, a reduction in attacks is clinically meaningful. The frequency of attacks was reported descriptively for each of the individual components, which highlighted some variability in the treatment benefit associated with givosiran compared with the composite outcome. Variation in clinical practice and the potential for unblinding or deduction of treatment allocation may have also biased treatment, which would impact the results of the individual components. As a result, there is notable uncertainty regarding the ability to interpret the individual components of the composite end point, but the estimates of effect for each of the components were in the same direction and were not expected to have impacted the overall composite outcome. A number of secondary outcomes were included and controlled for multiplicity using a statistical testing hierarchy; however, a failed statistical test for the change from baseline in daily worst pain rendered all subsequent secondary outcomes unadjusted for multiple testing. This included the evaluation of nausea, fatigue, and HRQoL via the PCS of the SF-12, which were all outcomes that were clinically relevant and important to patients. Further, all other HRQoL outcomes were exploratory and without an identified disease-specific minimally important difference, which hindered the interpretability of the results. Regarding the generalizability of the pivotal trial results, 95% of the study population were patients with AIP, 1 of the 4 types of AHP; however, according to the clinical experts, there is no biologic a priori reason to expect that the observed results are not generalizable to different AHP types. According to the sponsor, "the study was enriched for attack frequency to ensure the ability to measure a difference in treatment effect on the primary composite porphyria attack endpoint." The higher historical frequency of attacks at baseline for patients included in ENVISION and the inclusion criterion of at least 2 attacks in the past 6 months at baseline may limit the generalizability of the results to patients with less frequent attacks, which represents most patients in clinical practice according to the clinical experts on this review.

Indirect Comparisons

Indirect treatment evidence for givosiran was not identified in this review.

Other Relevant Evidence

Study 001 and Study 002

Description of Studies

Study 001 was a 3-part, multi-centre, placebo-controlled, phase I study of the safety and tolerability of subcutaneous givosiran for treatment of adults with AIP. Parts A, B, and C were single-ascending dose, multiple-ascending dose, and multidose in design, respectively. The adaptive design allowed for different dosing regimens and dose levels to be assessed based on new safety, tolerability, and pharmacodynamic data. In total, 40 patients with AIP who were chronic high excreters were randomized to parts A and B (n = 23), while those with AIP who had recurrent attacks were randomized to part C (n = 17). Data were summarized for patients who received givosiran 2.5 mg/kg (part A: n = 3, part C: n = 3). Patients in the 2.5 mg/kg cohort of part C had a mean of 14.7 (SD = 18.9) attacks in the 12 months before the study and one-third of patients were on prophylactic hemin.

Study 002 (N = 16) is an ongoing, multi-centre, open-label, phase I/II study of the long-term safety and tolerability of subcutaneous givosiran for treatment of adults with AIP who completed Study 001 part C. Patients received givosiran 2.5 mg/kg every month or 5.0 mg/kg every month or every 3 months until the safety review committee assessed safety, tolerability, and efficacy data and agreed that all patients would be transitioned to receive a 2.5 mg/kg dose. Treatment duration is estimated to be up to 36 months, and the estimated total time in the study with screening and baseline will be up to 44 months. Nearly all patients (93.8%) in Study 002 had at least 1 porphyria attack in the 12 months preceding the study, with a mean of 13.0 (SD = 13.1) porphyria attacks during that time period. All patients had used hemin during an acute attack during that 12 months, and half had used it prophylactically.

Efficacy Results

In Study 001, patients had fewer attacks during the treatment and follow-up phase compared with the run-in phase of part C for all attacks, attacks requiring hospitalization and urgent health care visits. The cohort receiving givosiran 2.5 mg/kg each month had a mean AAR of 2.9 (SEM = 1.91) for composite attacks and a mean annualized rate of hemin use of 2.9 (SEM = 1.44) days during the treatment and follow-up period. The placebo group had a mean AAR of 16.7 (SEM = 4.97) for composite attacks and a mean annualized rate of hemin use of 23.4 (SEM = 9.9) days during the treatment and follow-up period.

In Study 002, patients had fewer composite attacks during the treatment period compared with the run-in period (n = 9 and n = 72, respectively) and fewer attacks requiring hospitalization, urgent health care visits, and treatment with hemin at home. The mean composite AAR was 17.0 (SEM = 3.5) and 1.2 (SEM = 0.4) for the run-in phase to Study 001 part C and the treatment period, respectively. The mean rate for annualized hemin use was 33.1 (SEM = 7.0) days during the run-in period compared with 1.1 (SEM = 0.6) days during the treatment period of Study 002.

HRQoL was also assessed using the EQ-5D-5L in Study 001 and Study 002.

Harms Results

Most patients (66.7%) in Study 001 part A and 100% of patients in both Study 001 part C and Study 002 experienced at least 1 AE. In Study 001 part C, the most frequently reported AEs were abdominal pain, abdominal distension, nausea, and injection site reaction. In Study 002, the most commonly reported AEs were abdominal pain, fatigue, nausea, and injection site reaction. SAEs were reported in 100% of patients who received givosiran 2.5 mg/kg in part C and 25% of those in Study 002. SAEs included functional gastrointestinal disorder, pyrexia, anaphylactic reaction, *Clostridium difficile* colitis, sinusitis bacterial infection, mental status changes, dyspnea, and deep vein thrombosis. There was 1 withdrawal due to an AE in Study 002 and no deaths reported in the cohorts of interest.

Critical Appraisal

Key limitations of Study 001 include the single-blind, adaptive study design. Study 002 was limited by an open-label study design that selected for patients who were able to tolerate and adhere to treatment, which may bias the results in favour of givosiran. Both studies had small samples sizes, and only a couple patients were randomized to receive givosiran 2.5 mg/kg, the intended commercial dose, for a short duration of time.

Study 003 (ENVISION) Open-Label Extension Period

Description of Studies

The 6-month, double-blind, placebo-controlled ENVISION was followed by an ongoing, open-label extension (OLE) period that will be referred to as Study 003 OLE. The OLE phase of the study is expected to continue for 29 months and was designed to evaluate the long-term efficacy and safety of givosiran for treatment of adults with AIP. Patients who completed the double-blind portion of ENVISION (N = 94) were eligible to participate in the OLE phase. The baseline characteristics of patients included in the OLE were similar to those reported for the double-blind treatment period, with a slightly higher mean historical AAR of 11.6 (SD = 9.0) and prior prophylactic hemin use, reported by 44.2% of patients. Initially, patients received either 1.25 mg/kg or 2.5 mg/kg givosiran, but with protocol amendment 5 (after the cut-off date for the interim report), all patients received the latter dose.

Efficacy Results

After 18 months, the median follow-up, the mean (SEM) number of attacks during givosiran treatment was 3.4 (0.7) and appeared to be stable over time following treatment with givosiran. Mean (SEM) AARs for attacks requiring hospitalization, urgent health care visit, treatment with IV hemin at home, and treatment without IV hemin at home were [redacted], and [redacted], respectively. The mean (SEM) number of days of hemin use was [redacted] days. Urinary levels of ALA decreased from baseline by a mean (SD) of [redacted] mmol/mol Cr and [redacted] mmol/mol at months 12 and 18, respectively. Urinary levels of PBG also decreased by an average (SD) [redacted] mmol/mol and [redacted] mmol/mol for the same time points from baseline. Patient-reported outcomes including the SF-12, EQ-5D-5L, PGIC, and PPEQ, as well as daily worst symptom scores were also reported during the OLE and were consistent with the results described in the double-blind treatment period.

Harms Results

Nearly all patients (94.8%) experienced at least 1 AE, with 32.5% reporting nausea, 27.3% injection site reaction, 22.1% fatigue, 22.1% nasopharyngitis, and 19.5% headache. SAEs occurred in 24.7% of patients, with chronic kidney disease, device breakage, and urinary tract infection, each of which were reported in 2.6% of the patients. There was 1 withdrawal due to an AE, and no deaths were reported.

Critical Appraisal

Study OLE was subject to most of the limitations associated with the double-blind treatment period. Additional limitations of the extension period of ENVISION include the lack of a randomized comparison group and the open-label design, which may have influenced patients' and clinicians' perception of improvement and may be reflected in the patient-reported and safety outcomes. There was also a dose change for those who initially enrolled under protocol amendment 3 and received givosiran 1.25 mg/kg. At month 13, patients who had inadequate disease control were able to increase their dose from 1.25 mg/kg to 2.5 mg/kg, and with protocol amendment 5, all patients were to receive givosiran 2.5 mg/kg (the intended commercial dose).

Study 005

Study 005 is an international program that will provide expanded access to givosiran to patients 12 years and older with AHP. It is ongoing, and no additional information was available for this review.

Economic Evidence

Table 2: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with a documented diagnosis of AHP
Treatment	Givosiran
Submitted drug price	Givosiran, 189 mg/mL, solution for subcutaneous injection: $64,454.30 (price per carton containing 1 single-use 2-mL vial, which holds 1 mL givosiran sodium in solution)
Annual cost	At the recommended dose of 2.5 mg/kg monthly, and assuming a patient weight of 67 kg, the average annual cost of givosiran is approximately $773,448 for a patient.
Comparator	BSC: No treatment
Perspective	Canadian publicly funded health care payer
Outcome	QALYs; life-years
Time horizon	Lifetime (defined as 59 years)
Key data source	ENVISION trial
Submitted results	Givosiran was dominant — associated with more QALYs (a gain of 13.23) and less costly (savings of $8,658,644) — compared with BSC
Key limitations	• Clinical expert feedback indicated that AHP disease severity was not appropriately conceptualized by the sponsor because all attacks were considered to be equal in nature and the mean number of annualized attacks in the severe health state ([redacted] attacks) in the model was unrealistic. This led to an overestimation of health care resource use, particularly for patients on BSC. • There is no evidence available to support a QALY benefit with givosiran due to a reduction in long-term AHP-related chronic conditions as assumed by the sponsor. • The long-term efficacy of givosiran is uncertain because there are only data available for up to 18 months. More than 98% of the benefit with givosiran is from the period for which there is no observed data. Additionally, the sponsor's efficacy assumptions in the model overestimated the relative reduction in attacks with givosiran versus BSC when compared with the trial data. • Asymptomatic patients who discontinued givosiran at any point in time for reasons other than menopause did not experience any probability of future recurrent attacks but instead were assumed to maintain clinical benefit from treatment over their lifetime. This is an unrealistic assumption favouring givosiran because total costs are underestimated. • Female patients who experienced attacks just before the onset of menopause were assumed to continue experiencing attacks post-menopause, which was inconsistent with clinical expectations of the impact of menopause on the natural history of AHP. This overestimated the number of attacks experienced post-menopause, particularly for female patients on BSC. • The sponsor did not consider the potential for differences in the rate of reduction of attacks with givosiran by care setting (i.e., those requiring hospitalization or an urgent health care visit). This may have introduced uncertainty into the estimates of cost-effectiveness with givosiran, as attacks treated in hospital have different costs than attacks treated in urgent care.

Component	Description
	• CADTH also identified several other limitations that introduce uncertainty and may bias the results in favour of givosiran, including the amount of hemin required during urgent health care visits, the mean duration of a porphyric attack, assumptions around opioid addiction in AHP, baseline patient characteristics not aligning with the Canadian population, the inclusion of caregiver utilities, and misalignment between the probabilistic and deterministic results.
CADTH reanalysis results	• CADTH conducted reanalyses that included removing the severe health state, revising health state utility values to reflect a similar disutility due to chronic conditions for all patients, assuming all patients remained on givosiran from the end of the OLE period (18 months) until death, assuming that all female AHP patients who experienced attacks just before menopause onset became asymptomatic at the onset of menopause, changing the amount of hemin to 1 vial per urgent health care visit, changing the mean duration of an acute attack, setting the proportion of patients with an opioid addiction to 0%, revising the mean starting age and proportion of female patients to reflect the baseline characteristics of the trial population, and removing caregiver disutilities. CADTH also presented results deterministically due to issues with the sponsor's probabilistic analyses that could not be addressed. • Based on the CADTH reanalyses, the ICER for givosiran versus BSC is $17,928,198 per QALY gained. A 63% price reduction was required for givosiran to be considered cost-effective at a $50,000 per QALY threshold. • When considering a scenario restricted to patients with recurrent AHP, the ICER for givosiran versus BSC is $14,211,820 per QALY gained. A 57% price reduction was required for givosiran to be considered cost-effective at a $50,000 per QALY threshold. • Importantly, the cost-effectiveness of givosiran was driven by the price of givosiran and factors affecting both the frequency of acute attacks for patients on BSC and their associated costs.

AHP = acute hepatic porphyria; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; OLE = open-label extension; QALY = quality-adjusted life-years.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the anticipated market uptake of givosiran was underestimated, there is uncertainty around the estimates used to derive the size of the population eligible for treatment with givosiran, and adjustment of treatment costs by patient adherence is likely inappropriate and underestimated costs associated with givosiran. In reanalyses, CADTH updated the market share assumptions to align with expectations and assumed 100% treatment adherence. From the drug plan perspective, the anticipated budget impact from the introduction of givosiran was $60,329,225 in year 1, $60,329,225 in year 2, $61,102,676 in year 3, for a total budget impact of $181,761,126 over the 3-year time horizon. From a public health care payer perspective, which included drug administration costs and the costs of treating acute attacks, the total budget impact was estimated to be $129,996,431. CADTH was unable to address limitations related to the uncertainty around the estimated population size eligible for givosiran. Significant changes in population size would be associated with changes in the budget impact, as shown in a scenario analysis assessing an increase in the diagnosis rate.

CADTH

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: July 21, 2021

Regrets: None

Conflicts of interest: None