BRITISH COLUMBIA | Ministry of Health

Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**givosiran**
Brand Name	Givlaari™
Dosage Form(s)	Solution for subcutaneous injection
Manufacturer	Alnylam Netherlands B.V.
Submission Type	**New Submission**
Use Reviewed	Treatment of acute hepatic porphyria (AHP) in adults.
Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews (CRR)	Yes, CRR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CRR website for more details: http://www.cadth.ca/sites/default/files/DRR/2021/SR0679%20Givlaari%20-%20CADTH%20Final%20Rec-pw.pdf
Drug Benefit Council (DBC)	The DBC met on October 1, 2021. In their review, the DBC considered the following: the final reviews completed by CADTH on September 24, 2021, which included clinical and pharmacoeconomic evidence review material and the recommendations from the CRR. The DBC received no Patient Input Questionnaire responses from patients, caregivers, or patient Groups and so patient input provided to CADTH was also considered, as was a Budget Impact Assessment.

givosiran (Givlaari™)

	The DBC recommended that givosiran not be listed at the submitted price.
Drug Coverage Decision	**Case-by-Case Coverage Through the Expensive Drugs for Rare Diseases (EDRD) Process**
Date	June 22, 2023
Reason(s)	**Drug coverage decision is consistent with the CDEC and DBC recommendations.** • Evidence suggests givosiran resulted in a decrease in the annualized porphyria attack rate. • Based on economic considerations and the submitted product price, the drug was not cost effective and did not offer optimal value for money. • BC participated in the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations with the manufacturer and the pCPA was able to address the concerns identified by CADTH with respect to the cost-effectiveness and value for money. The negotiations concluded with an agreement on April 26, 2023.
Other Information	See the DBC Recommendation & Reasons

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews(CRR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Appendix

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Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Givosiran (Givlaari™)
Alynlam Netherlands B.V.

Description:

Drug review of **givosiran (Givlaari™)** for the following Health Canada approved indications:

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

In their review, the DBC considered the following: the final reviews completed by the Canadian Agency for Drugs and Technologies in Health (CADTH) on September 24, 2021, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC received no Patient Input Questionnaire responses from patients, caregivers, or patient Groups and so patient input provided to CADTH was also considered, as was a Budget Impact Assessment.

Dosage Forms:

Givlaari™ is available as givosiran subcutaneous injection in 1mL single use vial/189mg per mL.

Recommendations:

1. The Drug Benefit Council (DBC) recommends not to list givosiran (Givlaari™) at the submitted price nor with the criteria suggested by CADTH.

Of Note:

- Given the limited evidence of clinical efficacy, the drug requires further study to understand its impact on patients and its potential impact on the formulary.

DBC Meeting – October 1, 2021
DBC Recommendation and Reasons for Recommendations
DBC members present: Andrea Jones, Barbara Kaminsky, Bashir Jiwani, Bob Nakagawa (Chair), Charley Zhang, Dean Regier, Fawziah Lalji, Justin Chan, Karin Jackson, Peter Zed (Vice Chair), Ross Taylor

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Reasons for the Recommendation:

1. **Summary**

- Evidence from one randomized clinical trial demonstrated that givosiran resulted in a decrease in the annualized porphyria attack rate compared with placebo.
- Health-related quality of life measures either did not show a statistically significant result or were outside of the statistical testing hierarchy and not adjusted for multiple testing. As a result, there is no evidence of a quality of life improvement.
- The comparative efficacy and safety of givosiran is limited to the 6 months duration of ENVISION.
- At the manufacturer-submitted price, givosiran is not considered cost-effective for the indicated population.

2. **Clinical Efficacy**

- The DBC considered the CADTH systematic review, which included one multicenter, placebo-controlled, double-blind, phase III study, Study 003 (ENVISION).
- ENVISION was designed to evaluate the efficacy and safety of givosiran administered once monthly in patients with AHP. Patients enrolled in the study had a documented diagnosis of acute intermittent porphyria (AIP), coproporphyria (HCP), or variegate porphyria (VP) and had recurrent attacks requiring hospitalization, urgent healthcare visit or intravenous (IV) administration of hemin at home.
- The primary objective of ENVISION was to evaluate the effect of subcutaneous givosiran compared to placebo in terms of the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home over 6 months in patients with AIP.
- The mean annualized attack rate (AAR) based on the composite endpoint was 3.22 and 12.52 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. 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, and an 84% rate reduction in attacks requiring an urgent healthcare visit.
- Health-related quality of life was evaluated using the 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 failed to show a statistically significant result or were outside of the statistical testing hierarchy and not adjusted for multiple testing. 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 neurological or psychiatric complications of AHP.

- The comparative efficacy and safety of givosiran is limited to the 6 months duration of ENVISION. Data up to 36 months exists in the form of open label, non-comparative, extension studies, where evidence of efficacy and safety is limited in quantity and quality.
- For detailed information on the systematic review of givosiran please see the CDEC Final Recommendation at: https://www.cadth.ca/givosiran.

3. Safety

- In ENVISION, 85% of patients with AIP experienced at least one adverse event. 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 one 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).
- As above, the comparative efficacy and safety of givosiran is limited to the 6 months duration of ENVISION.
- For detailed information on the safety and tolerability of givosiran, please see the CDEC Final Recommendations at the links above.

4. Economic Considerations

- At the manufacturer-submitted price, treatment with Givlaari is expected to cost $64,454.30 per vial, or approximately $773,448 per patient per year, assuming patient weight is below 75.7 kg. Patients over 75.7 kg may require two vials per month, which would double the cost.
- The CADTH reanalysis of the incremental cost-effectiveness ratio (ICER) for givosiran, in patients with AHP with recurrent attacks, was over $14.2 million per quality-adjusted life-year (QALY) compared with best supportive care (BSC).
- CADTH recommended that a reduction in price of at least 57% would be required for givosiran to be considered cost-effective.

5. Of Note

- AHP is a family of rare genetic disorders that cause altered enzyme activity in the liver that 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 with recurrent acute attacks may include chronic pain, chronic kidney failure and liver damage.
- The patient groups who provided input to CADTH indicated their hope for 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, an easier mode of administration, can be administered outside of a hospital, and lead to improvements in quality of life.