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	**sodium phenylbutyrate and ursodoxicoltaurine (PB-TURSO)**
Brand Name	Albrioza™
Dosage Form(s)	Powder for oral suspension, 3g/1g sachet
Manufacturer	Amylyx Pharmaceuticals Inc.
Submission Type	**New Submission**
Use Reviewed	For the treatment of patients with amyotrophic lateral sclerosis (ALS).
Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews (CRR)	Yes, the CRR recommended **to Reimburse with clinical criteria and/or conditions.** Visit the CRR website for more details.
Drug Benefit Council (DBC)	The DBC met on August 15, 2022. In their review, the DBC considered the following: the final reviews completed by the CRR on July 21, 2022, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from 24 patients, four caregivers, and one patient group, as well as patient input provided to the CDEC and a Budget Impact Assessment. The DBC recommended that PB-TURSO not be listed for the treatment of ALS.

sodium phenylbutyrate and ursodoxicoltaurine (Albrioza™)

Drug Coverage Decision	**Limited Coverage Benefit**
Date	July 19, 2023
Reason(s)	**Drug coverage decision is consistent with the CDEC recommendation.** • Evidence from a phase II, double-blind, placebo-controlled clinical trial demonstrated that treatment with PB-TURSO slowed decline in physical function in patients with a diagnosis of definite ALS who were within 18 months of symptom onset. • However, the DBC noted that there were no statistically significant differences for PB-TURSO versus placebo found for any secondary end points, including survival outcomes. • Concerns were also noted about the trial, which enrolled small number of patients, with a short duration, and a high number of withdrawals. All efficacy and safety outcomes had missing data, leading to uncertainty in the results. • In addition, based on economic considerations and the submitted product price, PB-TURSO was not cost-effective and did not offer optimal value for money. • The Ministry of Health (the Ministry) took into consideration that ALS is a rare, progressive, life-threatening disease for which there are no treatments to stop or reverse disease progression. Patients expressed a need for treatments that significantly slow progression, help them maintain independence, and improve survival. • BC participated in the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations with the manufacturer. The pCPA was able to address the concerns identified by CADTH and the DBC with respect to the cost-effectiveness and value for money. The negotiations concluded with an agreement on June 12, 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

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Sodium phenylbutyrate and ursodoxicoltaurine (Albrioza®)
Amylyx Canada

Description:

Drug review of sodium phenylbutyrate and ursodoxicoltaurine (Albrioza®) for the following Health Canada approved indications:

For the treatment of amyotrophic lateral sclerosis (ALS).

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on July 21, 2022, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from 24 patients, 4 caregivers, and one patient groups, as well as patient input provided to the CDR and a Budget Impact Assessment.

Dosage Forms:

Albrioza® is available as individual sachets, each containing 10 g of powder (3 g sodium phenylbutyrate and 1 g ursodoxicoltaurine) to be reconstituted in 250 mL of room temperature water and taken orally or administered via feeding tube.

Recommendations:

1. The Drug Benefit Council (DBC) recommends that sodium phenylbutyrate and ursodoxicoltaurine (Albrioza®) not be listed.

Reasons for the Recommendation:

Summary

- Results of a phase II, multi-centre, double blind, placebo-controlled randomized controlled trial (RCT) to assess the safety, tolerability, and efficacy of sodium phenylbutyrate and ursodoxicoltaurine (PB-TURSO) in adult patients with ALS showed a statistically significant improvement in rate of change in one measure of disease progression.

- There were no statistically significant differences for PB-TURSO versus placebo found for any secondary end points, including survival outcomes.
- The RCT was a phase II trial with a small number of patients, a short duration, and a high number of withdrawals. All efficacy and safety outcomes had missing data, leading to uncertainty in the results.
- The Health Canada Notice of Compliance is conditional on the results of trials to verify its clinical benefit. When further trials are completed, the manufacturer can resubmit the data to CADTH for review.

Clinical Efficacy

- The DBC considered the CADTH Clinical Review report, which included the CENTAUR trial (N=137), a phase II, multi-centre, double blind, placebo-controlled RCT to assess the safety, tolerability, and efficacy of PB-TURSO in adult patients with ALS.
- The primary safety outcome of CENTAUR was to confirm the safety and tolerability of PB-TURSO while the primary efficacy outcome was the rate of change (slope) of disease progression as measured by the ALS Functional Rating Scale–Revised (ALSFRS-R).
- Secondary outcomes included in the CADTH review protocol were the accurate test of limb isometric strength (ATLIS) for measuring isometric muscle strength, slow vital capacity (SVC) percent predicted normal (PPN) for respiratory function, and survival (defined as death, tracheostomy or permanent assisted ventilation) outcomes.
- In CENTAUR, there was a statistically significant improvement in rate of change in the ALSFRS-R total score with PB-TURSO corresponding to a between-group difference in change from baseline to week 24 of 2.32 points. There was some uncertainty in the magnitude of the treatment effect due to the amount of missing data, with 75% of patients in the primary analysis population contributing data at week 24. Although there are no minimal important difference (MID) estimates available for the ALSFRS-R total score, the treatment effect was considered to be clinically meaningful according to CADTH clinical expert opinion.
- There were no statistically significant differences for PB-TURSO versus placebo found for any secondary end points (including ATLIS, SVC, and survival outcomes) in CENTAUR. Health-related quality of life and impacts on caregiver burden were not evaluated.
- CENTAUR was a phase II trial with a small number of patients and a short duration. Large proportions of patients discontinued from the study and the number of patients available for the analysis at 24 weeks varied largely from the number of patients randomized at baseline. All efficacy outcomes had missing data, including the ALSFRS-R total score at week 24 due to patients discontinuing from the study (23% of the randomized population) leading to uncertainty in the results.
- For detailed information on the systematic review of sodium phenylbutyrate and ursodoxicoltaurine (Albrioza®) please see the CDEC Final Recommendation at: https://www.cadth.ca/sodium-phenylbutyrate-and-ursodoxicoltaurine.

Safety

- 86 patients (96.6%) in the PB-TURSO group and 46 patients (95.8%) in the placebo group experienced at least 1 treatment-emergent adverse event (TEAE) during CENTAUR. The 3 most frequently reported TEAEs in the PB-TURSO group were falls, diarrhea, and muscular weakness.
- In total, 23 serious AEs (SAEs) were reported in 11 patients (12.4%) from the PB-TURSO group and 8 patients (16.7%) from the placebo group. The SAEs reported in more than 1 patient included respiratory failure, bacteremia, and nephrolithiasis.
- Overall, 18 patients (20.2%) from the PB-TURSO group and 5 patients (10.4%) from the placebo group withdrew from the study medication due to a TEAE. The most frequently reported reasons were diarrhea (5.6%) in the PB-TURSO group (versus 0 in the placebo group) and respiratory failure (6.3%) in the placebo group (versus 0 in the PB-TURSO group).
- There were 7 deaths reported during CENTAUR in the safety population: 5 patients in the PB-TURSO group due to respiratory failure or respiratory arrest (3 patients), subdural hematoma (secondary to a fall; 1 patient), and diverticular perforation (1 patient) compared to 2 patients in the placebo group, both due to respiratory failure or respiratory arrest.
- For detailed information on the safety and tolerability of sodium phenylbutyrate and ursodoxicoltaurine (Albrioza®), please see the CDEC Final Recommendations at the links above.

Economic Considerations

- The CADTH reanalysis of the manufacturer submission resulted in an incremental cost-effectiveness ratio (ICER) for PB-TURSO vs. riluzole of $2,086,658 per quality-adjusted life-year (QALY), with a 0% probability of being cost-effective at a $50,000 per QALY threshold. CADTH indicated that price reductions of approximately 98% are required for PB-TURSO to achieve cost-effectiveness at this threshold.

Of Note

- ALS is a rare, progressive, life-threatening disease for which there are no treatments to stop or reverse disease progression. Patients expressed a need for treatments that significantly slow progression, help them maintain independence, and improve survival. Patients noted that the other available treatments—riluzole and edaravone—do not significantly slow the progression of ALS or improve survival.
- One patient who responded to the questionnaire reported having tried PB-TURSO, at their own expense. This patient reported that the drug significantly slowed the rate of progression of the disease.