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	**luspatercept**
Brand Name	Reblozyl®
Dosage Form(s)	lyophilized powder for solution for subcutaneous injection
Manufacturer	Celgene Inc., a Bristol Myers Squibb company
Submission Type	**New Submission**
Use Reviewed	For the treatment of myelodysplastic syndromes-associated anemia
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: Luspatercept (Reblozyl) (cadth.ca)
Drug Benefit Council (DBC)	The DBC met on May 18, 2022 and considered various inputs including: the final reviews completed by the Common Reimbursement Review (CRR) of the Canadian Agency for Drugs and Technologies in Health (CADTH) on December 7, 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 considered patient input provided to the CRR, responses to clinical questions from a specialist, and a Budget Impact Assessment.
Drug Coverage Decision	**Non-Benefit**

Date	March 14, 2023
Reason(s)	**Drug coverage decision is consistent with the DBC and CDEC recommendation.** • Results from one ongoing phase III, randomized, double-blind, placebo-controlled study (MEDALIST) demonstrated that treatment with luspatercept was superior to placebo in the primary endpoint of achieving red blood cell transfusion independence (RBC-TI) for at least 8 weeks or greater (any consecutive 56-day period) from week 1 to week 24. • Clinical experts indicated the results of the primary endpoint were not clinically meaningful, as patients would need to achieve transfusion independence for at least 16 weeks (not 8 weeks). • Limitations in the trial methodology mean the effect of luspatercept on other outcomes (health-related quality of life, overall survival, progression to acute myeloid leukemia, iron accumulation, iron chelation therapy use, and health care resource utilization) is unknown. • Based on economic considerations and the submitted product price, the drug was not cost effective and does not offer optimal value for money. The pan-Canadian Pharmaceutical Alliance (pCPA) negotiated with the manufactuer and adequate value was not achieved for British Columbia.
Other Information	In addition to the MDS indication, luspatercept is concurrently being reviewed for transfusion-dependent anemia associated with beta-thalassemia. On July 5, 2021, the Drug Benefit Council (DBC) recommended not to list luspatercept at the submitted price for the treatment of beta-thalassemia.

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

luspatercept (Reblozyl®)

Celgene Inc., a Bristol Myers Squibb company

Description:

Drug review of **luspatercept (Reblozyl®)** for the following Health Canada approved indications:

> For the treatment of adult patients with transfusion dependent anemia requiring at least two RBC units over 8 weeks resulting from very low- to intermediate-risk myelodysplastic syndromes (MDS) who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy.

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) of the Canadian Agency for Drugs and Technologies in Health (CADTH) on December 7, 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 considered patient input provided to the CDR, responses to clinical questions from a specialist, and a Budget Impact Assessment.

Dosage Forms:

Reblozyl® is available as luspatercept 25 mg and 75 mg powder for subcutaneous injection.

Recommendations:

1. The Drug Benefit Council (DBC) recommends not to list luspatercept (Reblozyl®).

Reasons for the Recommendation:

1. Summary

- Results from one ongoing phase III, randomized, double-blind, placebo-controlled study demonstrated that treatment with luspatercept was superior to placebo in terms of achieving transfusion independence for at least 8 weeks (i.e., any consecutive 56 days) from week 1 through week 24.
- Clinical experts indicated the results of the primary endpoint were not clinically meaningful. Limitations in the trial methodology mean the effect of luspatercept on other outcomes (health-related quality of life, overall survival, progression to acute myeloid leukemia, iron accumulation, iron chelation therapy use, and health care resource utilization) is unknown.
- Only about one quarter of the patients exposed to luspatercept had any apparent benefit.
- An estimated price reduction of 85% would be required for luspatercept to be considered cost-effective.

2. Clinical Efficacy

- The DBC considered the CDEC systematic review, which included one pivotal trial (MEDALIST, n=229), an ongoing phase III, randomized, double-blind, placebo-controlled study that aims to evaluate the efficacy and safety of luspatercept in adult patients for the treatment of RBC transfusion-dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy.
- The primary outcome of MEDALIST was the proportion of patients treated with luspatercept versus placebo who achieved red blood cell transfusion independence (RBC-TI) for at least 8 weeks or greater (any consecutive 56-day period) from week 1 to week 24.
- The two key secondary outcomes were the proportion of patients who achieved RBC-TI for at least 12 weeks or greater (any consecutive 84-day period) from week 1 to week 48 and the proportion of patients who achieve RBC-TI for at least 12 weeks or greater (any consecutive 84-day period) from week 1 to week 24.
- Red blood cell-transfusion independence (RBC-TI) of 8 weeks was observed in 37.91% of patients in the luspatercept group, compared with 13.16% of those in the placebo group, with an odds ratio favouring luspatercept of 5.06.
- For the key secondary efficacy outcomes of RBC-TI of 12 weeks at week 48 and week 24, a greater proportion of patients in the luspatercept treatment group achieved RBC-TI than the placebo group.
- For the key secondary outcome at week 48, 33.3% of the patients achieved RBC-TI for at least 12 weeks in the luspatercept treatment group and 11.84% of the patients in the placebo group, with an odds ratio favouring luspatercept of 4.04.
- For the key secondary outcome at week 24, 28.1% of patients achieved RBC-TI for at least 12 weeks in the luspatercept treatment group and 7.89% of the patients in the placebo group, with an odds ratio favouring luspatercept of 5.07.
- Clinical experts consulted by CADTH indicated the results of the primary endpoint were not clinically meaningful and results of the 48-week secondary endpoint are difficult to interpret due to study design.

- The effect size of the primary endpoint of transfusion independence for 8 weeks in the study was small, with a transfusion-independence of 8 weeks being obtained in only about 38% of patients with a differential response compared to placebo of about 25%; hence, only about one quarter of the patients exposed to luspatercept had any apparent benefit.
- None of the other endpoints evaluated in MEDALIST (health-related quality of life, overall survival, progression to acute myeloid leukemia, iron accumulation, iron chelation therapy use, and health care resource utilization) were controlled for multiplicity, and the effect of luspatercept on these outcomes is unknown.
- For detailed information on the systematic review of luspatercept please see the CDEC Final Recommendation at: https://www.cadth.ca/luspatercept-0.

3. Safety

- In MEDALIST, a higher number of patients in the luspatercept treatment group experienced adverse events such as fatigue, diarrhea, asthenia, nausea, and dizziness.
- CADTH identified thromboembolic events, hypertension, hepatic and renal adverse events, and neoplasms as safety concerns associated with luspatercept. Thromboembolic events were lower in the luspatercept treatment arm compared to the placebo group
- For detailed information on the safety and tolerability of luspatercept, please see the CDEC Final Recommendations at the links above.

4. Economic Considerations

- CADTH's reanalysis of the manufacturer's economic submission estimated the incremental cost-effectiveness ratio (ICER) of luspatercept compared with best supportive care (BSC) to be $623,219 per quality-adjusted life-year (QALY).
- CADTH estimated a price reduction of 85% from the manufacturer's submitted price would be required for luspatercept to be considered cost-effective at a $50,000 per QALY willingness-to-pay threshold.

5. Of Note

- Patient group input submitted to CADTH indicated that symptoms of MDS impact patients' quality of life through fatigue and infections, as well as through disruptions caused by the need for regular transfusions.
- Patients reported having tried numerous other treatments, most commonly blood transfusions, but also including chemotherapy, drug therapy, stem cell or bone marrow transplant, blood cell growth factor therapy, watch-and-wait approach, anti-thymocyte globulin therapy, and immunoglobulin therapy. None of the patients reported having tried luspatercept.
- Patients expected a new treatment to improve quality of life and to reduce the need for transfusions.