CADTH

CADTH Reimbursement Review

# CADTH Reimbursement Recommendation

(Draft)

Luspatercept (Reblozyl)

For the treatment of adult patients with red blood cell transfusion-dependent anemia associated with beta-thalassemia

Recommendation: Reimburse with Conditions


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Single Technology

# Luspatercept (Reblozyl — Celgene Inc., a Bristol Myers Squibb company)

Therapeutic Area: Beta-thalassemia associated anemia

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that luspatercept should be reimbursed for the treatment of adult patients with red blood cell (RBC) transfusion-dependent anemia associated with beta-thalassemia, only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One phase III, randomized, double-blind, placebo-controlled study (BELIEVE, N = 336) in adult patients with transfusion-dependent anemia associated with beta-thalassemia demonstrated that treatment with luspatercept in addition to best supportive care (BSC) was associated with a statistically significant and clinically meaningful reduction in transfusion burden compared with placebo. In the BELIEVE study, 21.4% of patients in the luspatercept group achieved an erythroid response, defined as at least a 33% reduction from baseline in RBC transfusion burden, with a reduction of at least two RBC units during the protocol-defined period of 12 consecutive weeks (week 13 to week 24), compared with 4.5% of the patients in placebo group ($P < 0.0001$). Similarly, the proportion of patients who achieved an erythroid response of greater than or equal to a 50% reduction from baseline in transfusion burden in the same period was 7.6% in the luspatercept treatment group versus 1.8% in placebo group ($P < 0.05$). Patients expressed to CADTH the need for a treatment that reduces the burden and adverse effects of transfusion and improves health-related quality of life (HRQoL). Based on the evidence reviewed, luspatercept meets the need for reduction in transfusion burden, but no differences were observed on measures of HRQoL, and symptom reduction was not assessed.

The sponsor's submitted price of luspatercept is $2,189 per 25 mg and $6,567 per 75 mg. The recommended dose of luspatercept depends on treatment response; therefore, the average daily treatment ranges from $312.71 to $416.95, while the average annual cost of treatment is between $113,828 and $151,771 per patient. CADTH estimated the incremental cost-effectiveness ratio (ICER) of luspatercept compared with BSC to be $659,395 per quality-adjusted life-year (QALY), with a 0% probability of being cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold at the price submitted by the sponsor. A price reduction of 85% would be required for luspatercept to be cost-effective at this threshold. Scenario analyses were conducted to assess the impact of clinical uncertainty with luspatercept (examining the predictive value of serum ferritin, mortality benefit of luspatercept, and treatment durability of luspatercept). The scenario analyses resulted in ICERs greater than $1 million per QALY.

## Table 1. Reimbursement Conditions and Reasons

| Reimbursement Condition | Reason |
|---|---|
| **Initiation** | |
| 1. Adults with RBC transfusion-dependent anemia associated with beta-thalassemia. | The results of the BELIEVE study demonstrated that luspatercept is superior to placebo in reducing transfusion burden in adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia. |
| 2. Patients must be receiving regular transfusions, defined as:<br>2.1. 6 to 20 RBC units in the 24 weeks prior to initiating treatment with luspatercept, and<br>2.2. No transfusion-free period greater than 35 days in the 24 weeks prior to initiating treatment with luspatercept. | These conditions are based on the inclusion criteria of the BELIEVE study. |
| **Renewal** | |
| 1. Patients should be assessed for a response to luspatercept every 6 months.<br>1.1. An initial response to treatment is defined as a ≥33% reduction in transfusion burden (RBC units/time) with a reduction of at least 2 units versus the pre-treatment baseline burden (measured over 24 weeks prior to initiating treatment with luspatercept).<br>1.2. At each subsequent assessment, a reduction in transfusion burden of ≥33% compared to the pre-luspatercept transfusion burden must be maintained. | The duration of the BELIEVE study was not adequate to determine how long the treatment effect of luspatercept would be maintained. The definition of response to treatment as a ≥33% reduction in transfusion burden versus the pre-treatment baseline aligns with clinical expert opinion and the Health Canada product monograph. This definition is also consistent with the primary outcome used in the BELIEVE study. |
| **Discontinuation** | |
| 1. Luspatercept should be discontinued if a patient does not respond after nine weeks of treatment (three doses) at the maximum dose. A response is defined as per Renewal Condition 1.1. | The discontinuation of luspatercept after nine weeks is aligned with the Health Canada product monograph. |
| **Prescribing** | |
| 1. The patient should be under the care of a hematologist with experience in managing patients with beta-thalassemia. | Accurate diagnosis by a clinician with experience and expertise in treating and managing beta-thalassemia is important to ensure that luspatercept is prescribed only for appropriate patients and to ensure that patients receive optimal care and monitoring. |
| 2. The maximum dose of luspatercept should not exceed 1.25 mg/kg (or 120 mg total dose) per administration. | In the BELIEVE study, the dose levels were titrated stepwise up to a maximum of 1.25 mg/kg, and the maximum total dose per administration was not to exceed 120 mg. |
| **Pricing** | |
| 1. Price reduction | Based on CADTH re-analyses, the ICER of luspatercept plus BSC compared with BSC for patients with beta-thalassemia was $659,395 per QALY, with a 0% chance of being cost-effective at a |

| Reimbursement Condition | Reason |
|---|---|
| | WTP threshold of $50,000 per QALY. A price reduction of at least 85% is needed to meet the $50,000 WTP threshold. |

## Implementation Guidance

1. Regular access to a hematologist for luspatercept administration may be limited for some patients. There is potential for luspatercept to be administered by a healthcare professional in other settings, such as a community pharmacy.

## Discussion Points

- CDEC acknowledged that the current standard of care for managing beta-thalassemia requires clinic visits every 2 to 4 weeks for RBC transfusions and iron chelation therapy, and there are no other treatments available that address the underlying disease state. Luspatercept is the only approved treatment with evidence supporting a reduction in disease burden.
- CDEC discussed that results of the BELIEVE study may not be generalizable to patients with a diagnosis of HbS/beta-thalassemia or alpha-thalassemia as they were excluded from the study.
- Thromboembolic events, hypertension, hepatic and renal adverse events, bone pain, and neoplasms were identified as safety concerns associated with luspatercept, and these events occurred more frequently in the luspatercept group than in the placebo group in the BELIEVE study. The clinical expert noted that patients at an increased risk of thrombosis should be closely monitored while receiving treatment with luspatercept.

## Background

Luspatercept has a Health Canada indication for treatment of adult patients with RBC transfusion-dependent anemia associated with beta-thalassemia. Luspatercept is a recombinant fusion protein consisting of two identical chains, each consisting of a modified form of the extracellular domain of human activin receptor type IIB (ActRIIB) linked to the human immunoglobulin G1 (IgG1) Fc domain. Luspatercept is available as lyophilized powder for solution for subcutaneous injection in two strengths, 25 mg/vial and 75 mg/vial. The Health Canada recommended starting dose of luspatercept is 1 mg/kg up to a maximum of 1.25 mg/kg administered by a subcutaneous injection every 3 weeks.

## Summary of Evidence

To make their recommendation, CDEC considered the following information:

- A systematic review of 1 phase III randomized controlled trial (RCT) in adult patients with transfusion-dependent anemia associated with beta-thalassemia.
- Patients' perspectives gathered by patient groups, including the Thalassemia Foundation of Canada (TFC) and Canadian Organization for Rare Disorders (CORD).
- Input from 4 clinical specialists with expertise diagnosing and treating patients with transfusion-dependent anemia associated with beta-thalassemia.
- A review of the pharmacoeconomic model and report submitted by the sponsor

### Summary of Patient Input

Two patient groups, Thalassemia Foundation of Canada (TFC) and Canadian Organization for Rare Disorders (CORD), conducted focus groups and an online survey to solicit patient input. The following is a summary of key input from the perspective of the patient groups:

- Patients were most concerned with serious complications due to thalassemia or its treatment. Experience of iron overload that was not well managed by chelation was a serious problem for the patients. Approximately 30% of patients reported a “life-threatening” or “serious” experience of an enlarged spleen. Other complications experienced by patients included: liver damage

(hepatitis, fibrosis), infections, and hearing and vision sensitivities or loss, and psychological or emotional effects such as anxiety, depression, and panic attacks.

- Patients have a long-term exposure to blood transfusions and chelation, with many patients receiving treatment for decades. The cycle of transfusion is time-consuming, it interferes with work and school and is a burden to normal social and home life, and iron chelation is not only onerous but also limiting in terms of mobility. Moreover, prior to scheduled transfusion time, patients experience fatigue, low energy and decreased mental acuity associated with low hemoglobin. Children are unable to do sleepovers; families are restricted in terms of travel; and adults report limitations in terms of their work, social life, and overall quality of life. Overall, patients desire improvement in HRQoL, reduced adverse effects, and decreased burden of treatment.

## Clinical Trials

The CADTH systematic review included one ongoing phase III, multicentre, double-blind randomized placebo-controlled study (BELIEVE, N = 336) evaluating the efficacy and safety of luspatercept in adult patients with transfusion-dependent anemia associated with beta-thalassemia. The BELIEVE trial had a 12-week screening/run-in period during which the patient's prior 24-week transfusion history was documented. Following the 12-week screening/run-in phase, eligible patients were randomized (2:1) to receive either luspatercept or placebo along with BSC for 48-weeks in a double-blind manner. BSC included RBC transfusions, ICTs, antibiotic, antiviral, and antifungal therapies; and/or nutritional support as needed.

Patients received a starting dose of 1 mg/kg of the study drug administered by a subcutaneous injection every 3 weeks for 48 weeks. During this period the dose levels were titrated (increased) stepwise up to a maximum of 1.25 mg/kg or reduced based on a clinical response. The maximum total dose per administration was not to exceed 120 mg.

The baseline characteristics of the patients enrolled in the BELIEVE study were overall well balanced. The mean (SD) age of the patients was 32.2 (10.67) and 31.9 (9.89) in the luspatercept and placebo groups, respectively, and 58.9% of the patients in the luspatercept treatment group and 56.3% patients in the placebo group of the study were females. The percentage of patients who discontinued from the study was 12.5% in the placebo treatment group and 11.6% in the luspatercept treatment group.

The main limitations were potential for unblinding due to lack of efficacy or adverse events, missing data for some endpoints (i.e., HRQoL), and inadequate duration of the trial to demonstrate maintenance of the treatment effect of luspatercept in the long term.

## Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following: hematologic response, HRQoL, and iron accumulation.

*Hematologic Response*

Hematologic response was assessed by RBC transfusion burden, transfusion frequency and RBC units.

The primary outcome of BELIEVE was based was an erythroid response of greater than or equal to 33% reduction from baseline in transfusion burden (RBC units/time) with a reduction of at least two units, in the fixed 12-week period form week 13 to week 24. The secondary outcomes assessed an erythroid response greater than or equal to 33% reduction from baseline with a reduction of at least two units in the fixed 12-week period form week 37 to week 48, greater than or equal to 50% reduction with a reduction of at least two units in the fixed 12-week period from week 13 to week 24 and from week 37 to week 48, and the mean change from baseline in RBC transfusion burden to the fixed week 13 to week 24 interval.

*Health Related Quality of Life (HRQoL)*

HRQoL was assessed as mean change from baseline at week 24 and 48 using the SF-36 and TranQoL instruments.

The TranQoL Questionnaire is a disease-specific questionnaire for adults and children with thalassemia major that focuses on quality-of-life issues related to transfusion burden. The TranQoL assesses the following four domains: physical health, emotional health, family functioning, school and career functioning, and physical health. The total score and domain scores range from 0 (worst) to 100 (best). Internal consistency, test–retest reliability and reliability of individual TranQol domains were acceptable.

The ability for the TranQoL to detect a meaningful change in quality of life was determined as patients who rated their QoL as better had a 4.0-point (SD 9.0) improvement in TranQoL scores, from baseline of 67.1 to 71.1 points one week later (P = 0.008). A MID for the TranQol in patients with transfusion-dependent thalassemia was not identified in the literature.

The SF-36 is a 36-item, generic, self-reported questionnaire that is scored from 0 to 100 and has been used extensively in clinical trials in many disease areas. The SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. For each of the eight domains, a subscale score can be calculated. The SF-36 also yields 2 summary measures of physical health (the Physical Component Score [PCS] measure) and mental health (the Mental Component Score [MCS] measure) derived from scale aggregates. Higher global scores are associated with better quality of life. The scores can also be standardized to the general US population, where an average score is 50. Validity, reliability, and responsiveness for patients with transfusion-dependent thalassemia was not identified in the literature for the English version of the scale.

*Iron Accumulation*

Iron accumulation was assessed using LIC and myocardial iron concentration (MIC) using T2* MRI and were included in the CADTH review. The LIC was measured at three time periods – baseline, 24-weeks, and 48-weeks. MIC was measured at two time points: baseline and 48-weeks.

## Efficacy

In the BELIEVE study, the primary efficacy outcome demonstrated that a significantly greater proportion of patients treated with luspatercept exhibited at least a 33% reduction from baseline in transfusion burden during the fixed 12-week period from weeks 13 to 24 than in the placebo group. In the luspatercept treatment group 21.4% of the patients achieved the primary endpoint compared with 4.5% of the patients in placebo group (difference in proportions [95% CI] = 17.0 [10.4 to 23.6]; P < 0.0001).

In a fixed 12-week period from week 37 to week 48, 19.6% of the patients in the luspatercept treatment group and 3.6% of the patients in placebo group achieved an erythroid response of greater than or equal to 33% reduction from baseline in transfusion burden (units RBCs/time) with a reduction of at least 2 units (difference in proportions [95% CI] =16.1 [9.8 to 22.3]; P < 0.0001). The proportion of patients who achieved an erythroid response of greater than or equal to 50% reduction from baseline in transfusion burden (units RBCs/time) with a reduction of at least 2 units during the fixed 12-week period from week 13 to week 24 was 7.6% in the luspatercept treatment group, and 1.8% in placebo group (difference in proportions [95% CI] = 5.8 [1.6 to 10.1]; P = 0.0303). In the fixed 12-week period from week 37 to week 48 the proportion of patients who achieved an erythroid response of greater than or equal to 50% reduction from baseline in transfusion burden (units RBCs/time) with a reduction of at least 2 units, was 10.3% in the luspatercept group and 0.9% in the placebo group (difference in proportions [95% CI] = 9.4 [5.0 to 13.7]; P = 0.0017). The clinical experts consulted by CADTH suggested that the 33% or greater and 50% or greater reduction in transfusion burden were clinically meaningful outcomes.

Health-related quality of life as measured by the TranQoL and SF-36 were outside of the statistical testing hierarchy and were therefore considered as supportive evidence. Overall, luspatercept did not show benefit in terms of HRQoL when evaluated against the placebo treatment group.

Iron accumulation was measured through liver iron concentration, myocardial concentration, and serum ferritin. These outcomes were outside of the statistical testing hierarchy and hence were considered as supportive evidence. The iron accumulation was measured as a change from baseline. The clinical experts consulted by CADTH suggested that liver iron concentration and myocardial iron concentration were more reliable indicators of iron overload as compared to serum ferritin levels, as there are frequently large fluctuations with this measurement.

## Harms (Safety)

In BELIEVE, 96.0% and 92.7% of the patients in the luspatercept and placebo treatment group, reported at least one adverse event (AE) respectively. In the luspatercept treatment group 4% of the patients and 0.9% patients in the placebo group reported experiencing at least 1 thromboembolic event. The most commonly occurring AEs in luspatercept and placebo treatment group,

respectively, were back pain (27.4% and 29.4%), upper respiratory tract infection (26.5% and 33.0%), headache (26.0% and 23.9%), and bone pain (19.7% and 8.3%).

In BELIEVE, serious adverse events (SAEs) were reported 15.2% patients in the luspatercept treatment group and 5.5% patients in the placebo group. The most commonly reported SAE was infections and infestations, reported by 5.8% of patients in the luspatercept group and 2.8% of patients in the placebo group. The proportion of patients who stopped treatment due to an adverse event was 5.4% and 0.9% in the luspatercept and placebo treatment group, respectively.

One patient died in each treatment group.

## Cost and Cost-Effectiveness

Luspatercept is available at a cost of $2,189 per 25 mg and $6,567 per 75 mg powder. The recommended dose is between 1.0 and 1.25 mg/kg every three weeks, leading to an average daily cost of $312.71 to $416.95 per patient (or $113,828 to $151,771 annually).

The sponsor submitted a cost-utility analysis comparing luspatercept and best supportive care (BSC, consisting of RBC transfusions and ICT) compared to BSC alone, for the treatment of adult patients with transfusion-dependent anemia associated with beta-thalassemia. The modelled population aligned with the Health Canada indication and reimbursement request. A semi-Markov model was submitted which included a decision tree up to 48 weeks followed by a Markov model. The decision tree informed whether patients would be considered responders to luspatercept. The Markov model included mutually exclusive health states based on transfusion burden (complication-free), as well as states pertaining to cardiac, liver, and endocrine complications within these states, and a death state. Transitions into the complication states were based on hazard ratios associated with serum ferritin levels and complication states were associated with an increased risk of death. The model was run over the patient's lifetime (70 years).

The following key limitations were identified:

- Discrepancies in the data available for the CADTH clinical and pharmacoeconomic reviews made validating the clinical inputs challenging. First, the pharmacoeconomic model was based on a different data cut (July 2019) than the clinical review (May 2018). Second, the model population consisted of the North American/European subpopulation and not the full intention-to-treat population as provided for the clinical review. Third, the definition of 'response' to luspatercept differed between the model and that which was used in the BELIEVE clinical trial on which the model is based.
- There was uncertainty pertaining to some of the sponsor's assumptions given the lack of long-term clinical data. Specifically, uncertainty existed surrounding the durability of luspatercept response, the predictive ability of serum ferritin measurements, and assumptions around dose delays for luspatercept, which may or may not occur in clinical practice.
- The BELIEVE clinical trial considered a 'fixed' assessment window from week 13 to 24, and not a 'rolling' assessment (i.e., the reduction in RBC transfusion burden could occur at any time) as was used by the sponsor in their base case analysis.
- The utility values used by the sponsor are associated with uncertainty. The sponsor provided different estimates based on published sources. Based on feedback from the clinical experts consulted by CADTH, alternate values provided by the sponsor were felt to better represent patient preferences.

CADTH undertook reanalyses to address several key limitations of the sponsor's model, including: more conservative assumptions about luspatercept efficacy as well as transfusion burden for those receiving BSC after 48 weeks; alternative utility estimates; use of the full intention-to-treat population; increase to the average dose intensity; use of a 'fixed' response criteria; and, use of the January 2019 data cut of BELIEVE.

In the CADTH base case, the incremental cost-effectiveness ratio (ICER) was $659,395 per QALY compared with BSC. Based on CADTH reanalyses, the probability of luspatercept being cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 0%. A price reduction of at least 85% would be required for luspatercept to be cost-effective at this threshold.

A key driver of the analysis are the assumptions around the long-term use and effects of luspatercept. When exploring the impact of a loss of treatment efficacy after 5 years, luspatercept was dominated by BSC (luspatercept is associated with greater costs and less QALYs); and, after 10 years, the ICER for luspatercept compared with BSC was $1,352,159 per QALY. When the predictive nature of SF levels was removed the resulting ICER was $1,398,609 per QALY. And, when the mortality benefit of luspatercept was removed the resulting ICER was $1,198,773 per QALY. This highlights the impact of clinical uncertainty on the cost effectiveness of luspatercept.

## CDEC Members

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.

## April 21, 2021 Meeting

## Regrets

Three expert committee members did not attend.

## Conflicts of Interest

None

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