pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Blinatumomab (Blincyto)

Submitted Funding Request: For the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia

Submitted by:
Amgen Canada Inc.

Manufactured by:
Amgen Canada Inc.

Notice of Compliance Date:
December 22, 2015

Resubmission Date:
February 24, 2017

Initial Recommendation Issued:
June 29, 2017

pERC RECOMMENDATION	pERC recommends the reimbursement of blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) relapsed/refractory B precursor acute lymphoblastic leukemia (conditional on the cost-effectiveness being improved to an acceptable level). Treatment should be for patients with a good performance status and should be continued until unacceptable toxicity or disease progression, up to a maximum of 2 cycles for induction, 3 cycles for consolidation and 12 months for maintenance. pERC made this recommendation because it agreed there is a net clinical benefit of blinatumomab based on statistically significant and clinically meaningful improvement in overall survival and less deterioration in quality of life compared with chemotherapy. However, toxicity was increased with blinatumomab. pERC agreed that blinatumomab aligns with patient values. The Committee concluded that, at the submitted price, the high level of uncertainty in the magnitude of long term benefit and the incomplete accounting for complex resource intensity of administration, blinatumomab was not cost-effective in this population.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit of blinatumomab in patients with Ph- relapsed/refractory B precursor ALL, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of blinatumomab to an acceptable level. pERC noted that the cost of blinatumomab was extremely high and that drug price and estimates of long-term overall survival benefits were key drivers of the incremental cost-effectiveness estimates. Therefore, to offset the

considerable uncertainty in the clinical-effect estimates, pERC concluded that a substantial reduction in drug price would likely be required to improve cost-effectiveness.

Resource Use and Adoption Feasibility
pERC noted that the preparation, administration, and management of blinatumomab is resource-intensive. Therefore, pERC noted that jurisdictions will need to consider the incremental costs associated with, but not limited to, purchasing specialized infusion pumps, training pharmacy and nursing staff, coordinating outpatient and hospital resources, and monitoring and treating adverse events, all of which may require significant expenditures of human resources.

Wastage and Budget Impact Likely to Affect Adoption Feasibility
pERC also noted that the submitted model assumes vial-sharing in the first seven days of treatment and that all subsequent doses will use full vials. However, pERC expects that there may be considerable wastage with blinatumomab, given the challenges associated with implementing blinatumomab protocols (e.g. different infusion durations per preparation bag [between 24-96 hours], different pump infusion rates with different durations of infusion, etc.). pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation; this may include advocating for the availability of a smaller vial size.

Time-Limited Need for Blinatumomab
At the time of implementing a funding recommendation for blinatumomab, jurisdictions may consider addressing the time-limited need of blinatumomab for those patients who are currently receiving treatment with combination chemotherapy as a second or later salvage therapy. pERC noted that this time-limited access should be for patients who would otherwise meet the reimbursement criteria.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Approximately 15% of adult cases of acute leukemia involve acute lymphoblastic leukemia (ALL). Traditionally, age and cytogenetics have been viewed as the most important prognostic factors for ALL. Patients who present with an increased white blood cell count and those over age 34 are at higher risk of adverse outcomes. In contrast to upfront treatment, there is no standard treatment for patients with relapsed/refractory B precursor ALL. The prognosis for patients at this stage is poor and prolonged survival is rare for patients who fail to achieve remission with salvage chemotherapy. Available treatment options include salvage treatment (i.e., second-line treatment) with combination chemotherapy not used in upfront treatment (e.g., hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high-dose methotrexate and cytarabine), Flag-Ida, or Cy VP16, among others) to achieve remission and, if possible, proceed to potentially curative allogeneic hematopoietic stem cell transplant (allo-HSCT) in consolidation of remission. Patients who fail re-induction or for whom allo-HSCT is not feasible due to comorbidities or lack of a donor have no curative options and are treated with palliative intent. Survival of this cohort of relapsed/refractory patients is limited. Therefore, there is a continued need for effective treatment options that prolong patients' survival.

The Committee deliberated on the results of one randomized controlled trial, TOWER, which evaluated the efficacy and safety of blinatumomab compared with chemotherapy in adult patients with Philadelphia chromosome-negative (Ph-) relapsed/refractory B precursor ALL. pERC noted that the TOWER trial was stopped early due to a statistically significant improvement in overall survival (OS). The OS benefit was clinically meaningful and maintained within both the intention-to-treat and per-protocol analyses. pERC acknowledged that the OS benefit persisted between months 3 to 16 with the two arms of the Kaplan-Meier curves for OS converging completely by 15-18 months. . The Committee therefore agreed that there is uncertainty as to whether or not blinatumomab provides a long-term OS benefit. pERC also noted that quality of life (QoL) was maintained with blinatumomab compared with a decline in a number of QoL measures in the chemotherapy group. However, pERC acknowledged that QoL data were available only for the first 28 days of treatment, as most patients in the chemotherapy groups had stopped treatment in subsequent measurements. pERC noted a greater incidence of serious adverse events in the blinatumomab group compared with the chemotherapy group. Also, pERC noted the increased incidence of Grade 3 or 4 serious adverse events for cytokine release syndrome in the blinatumomab group, while none were reported in the chemotherapy group. Despite the increased toxicity profile of blinatumomab, pERC concluded that there is a net clinical benefit of blinatumomab compared with chemotherapy because of the statistically significant and clinically meaningful OS benefit and the maintenance of QoL.

The Committee deliberated on the patient advocacy group input, which indicated that patients with ALL value disease control and the management of side effects related to current therapies for ALL. Given improvements in OS and maintenance of QoL, pERC agreed that blinatumomab aligns with patient values overall. However, the Committee agreed the incidence of serious adverse events and cytokine release syndrome increase with blinatumomab.

pERC deliberated upon the cost-effectiveness of blinatumomab and concluded that blinatumomab is not cost-effective when compared with hyper-CVAD. The Committee noted that a number of clinical assumptions in the submitted model overestimated the long-term benefit anticipated with the use of blinatumomab. Specifically, pERC noted that the use of a 50-year time horizon, extrapolation of survival benefit beyond the trial period, and choice of parametric model used to extrapolate long-term survival all had a substantial impact on the incremental cost-effectiveness ratio (ICER). When the time horizon was set to 10 years to better reflect the expected clinical course of relapsed/refractory ALL, the OS benefit was restricted to the trial follow-up period, and an alternative parametric model chosen to fit the trial data, the ICER increased to nearly $1 million per quality-adjusted life year (QALY). Furthermore, in the submitted model, it was assumed that most of the blinatumomab administration would be in the outpatient setting. Given that jurisdictions have limited experience with blinatumomab administration to

date, many patients may have the majority of their blinatumomab treatment administered in-hospital and blinatumomab treatment on an outpatient basis may be limited to centers with infrastructure to support blinatumomab preparation and administration. pERC therefore agreed that the incremental cost of blinatumomab treatment is likely greater than incorporated in the economic model. Overall, pERC agreed that blinatumomab is not cost-effective and to offset the considerable uncertainty in the clinical effect estimates, a substantial reduction in drug price would likely be required.

The Committee discussed factors affecting the feasibility of implementing a reimbursement recommendation for blinatumomab. Various implementation and feasibility challenges were discussed, including, but not limited to, the requirement for considerable coordination of pharmacy and nursing staff training to prevent medication error for both inpatient and outpatient administration; the strict adherence and intensive staff training for the very complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer; and the required monitoring and treatment of toxicities. pERC further noted that blinatumomab preparation/administration, due to its complexity, may be limited to certain treatment centres with adequate resources (e.g. appropriate ambulatory infusion pump supply, adequate staffing). In addition, pERC noted that, for logistical reasons, many patients may be treated as inpatients beyond the initial cycles which will require coordination amongst inpatient and outpatient facilities and availability of on-call support. The complexity of blinatumomab was further discussed by pERC since a variety of concentrations/durations of stability are possible for blinatumomab preparations and it was noted that administration/preparation protocols for blinatumomab may be different amongst jurisdictions in order to accommodate local resources. Potential differences in protocol could impact upon potential drug wastage, particularly in centers that do not treat many patients and where vial sharing is not feasible. Based on these various challenges, pERC agreed that the implementation of blinatumomab will require considerably more expenditures and human resources than accounted for in the economic model provided by the submitter. pERC further agreed that the budget impact of blinatumomab will increase due to these various additional costs.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated on:

- A pCODR systematic review
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group (the Leukemia & Lymphoma Society of Canada (LLSC))
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of blinatumomab as a monotherapy compared with an appropriate comparator, on patient outcomes in the treatment of adults with Philadelphia chromosome–negative (Ph–) relapsed/refractory B precursor acute lymphoblastic leukemia (ALL).

Studies included: One randomized controlled trial

The pCODR systematic review included one randomized controlled trial, TOWER, which evaluated the efficacy and safety of blinatumomab compared with chemotherapy in adult patients with Philadelphia chromosome–negative (Ph–) relapsed/refractory B precursor acute lymphoblastic leukemia (ALL). Patients were randomized in a 2:1 ratio to blinatumomab (n=271) or to 1 of 4 standard of care chemotherapy regimens (n=134).

Blinatumomab was administered in six-week cycles for induction and consolidation and 12-week cycles for maintenance. During induction and maintenance, each cycle consisted of four weeks on treatment followed by two treatment-free weeks. During cycle 1 of week 1, patients received 9 µg/day as induction therapy followed by 28 µg/day for the remaining days of the four weeks of treatment. Maintenance treatment was given as a four-week continuous infusion every 12 weeks. Induction was given up to two cycles, consolidation up to three cycles and maintenance up to 12 months. Patients moved onto subsequent phases of treatment with blinatumomab based on having a greater than 5% blast count. Chemotherapy was provided using one of four regimens selected by the treating clinician investigators. The four treatment regimens used in the study included were 1) fludarabine, high-dose cytosine arabinoside, and granulocyte colony-stimulating factor with or without anthracycline; 2) a high-dose cytosine arabinoside-based regimen; 3) a high-dose methotrexate-based regimen; or 4) a clofarabine-based regimen. pERC noted that the comparators used in the trial are mostly applicable to the Canadian treatment landscape with the exception of clofarabine.

Patient populations: Well balanced between groups

Baseline characteristics were generally well balanced between treatment groups. The mean age of patients was 41 years, with 45% of patients being over the age of 35. Most patients enrolled had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 (35% and 39%) or 1 (49% and 46%) in the blinatumomab and chemotherapy groups, respectively. A minority of patients had an ECOG PS of 2 (15%) in both groups. Among enrolled patients, 35% and 34% had a previous allogeneic stem cell transplantation, while 42% and 49% had no prior salvage therapy in the blinatumomab and chemotherapy groups, respectively.

Among patients randomized to chemotherapy, 25 (18.7%) did not receive treatment with 22 of 134 (16.4%) not receiving study treatment at the patient's request. Despite this large proportion of patients not receiving assigned therapy, the demographics and trial results were similar between the intention-to-treat and per-protocol analysis for the primary outcome of overall survival (OS).

Key efficacy results: Overall survival benefit up to 18 months, long-term benefit uncertain

The key efficacy outcome deliberated on by pERC, and the primary outcome of the trial, was OS. A statistically significant and clinically meaningful improvement in OS was reported in favour of blinatumomab compared with chemotherapy (median OS: 7.7 months and 4.0 months, respectively;

hazard ratio = 0.71; 95% CI, 0.55 to 0.93, *P* = 0.01). The absolute magnitude of difference was 3.7 months in favour of blinatumomab. This benefit persisted between months 3 to 16 with the two arms of the Kaplan–Meier curves for OS converging completely by 18 months. The study was stopped early — at the recommendation of the independent data and safety monitoring committee after a planned interim analysis of 75% of the total number of required deaths — due to the benefit observed according to the O'Brien–Fleming stopping boundary.

The trial also reported that a similar proportion of patients (24%) underwent allogeneic stem cell transplantation in both groups. Censoring the OS results for stem cell transplant did not have an impact on the OS benefit. Given that the trial was not designed to evaluate the ability of blinatumomab to get patients to transplant, pERC agreed that only a limited conclusion could be drawn from these data. pERC noted that there could be various reasons, independent of treatment, why patients would not qualify for transplant and that a trial would be needed to determine the impact of blinatumomab on bridging patients to transplant.

Key secondary end points included complete remission with full hematological recovery within 12 weeks after initiation of treatment (33.6% versus 15.7%, *P* < 0.001) and complete remission with full, partial, or incomplete hematological recovery within 12 weeks of initiation of treatment (43.9% and 24.6%, *P* < 0.001) both of which were higher in the blinatumomab group.

Patient-reported outcomes: Maintained quality of life but short duration of measurement

Health-related quality of life (HRQoL) was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Time to deterioration (TTD) in HRQoL was reported and defined as the time from baseline to a 10-point deterioration in the EORTC QLQ-C30, or event-free survival. A 10-point change in deterioration or improvement in the EORTC QLQ-C30 was used to define a minimal important difference.

Functional scores and symptom scales on the EORTC QLQ-C30 demonstrated a meaningful change from baseline with blinatumomab. In the chemotherapy group, a clinically meaningfully decline was reported in the chemotherapy group for physical, role, and social functioning. A clinically meaningful decline was also reported in the chemotherapy group for fatigue, pain, nausea and vomiting, appetite loss, and diarrhea on the symptom scale. TTD also favoured blinatumomab for global health status and quality of life (QoL); physical, role, cognitive, emotional, and social functioning; and all symptom scores except insomnia and fatigue. QoL data from the TOWER study were only acquired up to a maximum of three months in the chemotherapy arm following randomization.

The Committee noted that quality of life was maintained with blinatumomab compared with a decline in a number of scores in the chemotherapy group. However, pERC agreed that the long-term impact of blinatumomab on patient QoL is unknown, given that most of the data on QoL was based only on the first 28 days of treatment. pERC noted that improvements of disease symptoms and treatment-related side effects were meaningful to patients. Input from registered clinicians also supports the findings that blinatumomab results in improvement of patient QoL. Overall, pERC agreed that the observed maintenance of patient QoL with the use of blinatumomab is a meaningful outcome.

Safety: Increased toxicity

The Committee discussed the adverse events observed in the TOWER study. Fatal adverse events occurred in a similar proportion of patients (19% and 17%) in the blinatumomab and chemotherapy groups, respectively. Grade 3 or 4 adverse events were also comparable between the two treatment groups (86.5% and 91.7%, respectively). Serious adverse events (SAEs) occurred more frequently in the blinatumomab group compared with chemotherapy (62% and 45%). %). However when adjusted for length of exposure the serious adverse event rates were 349.4 per 100 patient years in the blinatumomab group versus 641.9 per 100 patient years in the chemotherapy group. Cytokine release syndrome was reported in 13 (4.9%) patients receiving blinatumomab, with no treatment interruptions required. Of these, seven (2.6%) were considered SAEs. Cytokine release syndrome did not occur in the chemotherapy group. Grade 3 or 4 infections occured less frequently with blinatumomab, while serious infections and infestations were similar between groups. Blinatumomab is also associated with a unique and potentially severe neurologic side effect profile (e.g., encephalopathy or psychiatric disorders). Based on the trial results, grade 3 or higher neurological events were reported in 25 (9.4%) and 9 (8.3%) of patients in the blinatumomab and chemotherapy groups, respectively. Discontinuation due to neurologic events occurred in 4% and 1% of treated patients, respectively.

The Committee also discussed the toxicity profile of blinatumomab and agreed that it is increased compared with chemotherapy. pERC noted that patients desire better control of treatment-related side effects, and so the increased incidence of SAEs and cytokine release syndrome will need to be considered by patients and treating oncologists/hematologists.

Need and burden of illness: Need for prolonged survival

ALL represents approximately 15% of adult cases of acute leukemia. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL. Patients who present with an increased white blood cell count and those over age 34 are at higher risk of adverse outcomes. In contrast to upfront treatment, there is no standard treatment for patients with relapsed/refractory B precursor ALL. The prognosis of patients at this stage is poor and prolonged survival is rare for patients who fail to achieve remission with salvage chemotherapy. Available treatment options include salvage treatment (i.e., second-line treatment) with combination chemotherapy not used in upfront treatment (e.g., hyper-CVAD, FLAG-Ida, or Cy VP16, among others) to achieve remission and if possible, proceed to potentially curative allogeneic hematopoietic stem cell transplant (allo-HSCT) in consolidation of remission. Regimens used for re-induction are reported to be successful 40% to 60% of the time, with slightly higher rates reported for patients treated after first relapse than later in the disease course. Relapsed/refractory ALL patients are encouraged to proceed to allo-HSCT at the earliest opportunity as a cure is not expected with salvage therapy alone. Patients who fail re-induction or for whom allo-HSCT is not feasible due to comorbidities or lack of a donor have no curative options and are treated with palliative intent. Survival of this cohort of relapsed/refractory patients is limited and there is a continued need for treatment options that prolong patients' survival.

Registered clinician input: Need for effective treatments

The Committee deliberated on input from one clinician. Based on this input, the occurrence of ALL is low. Current standard options in the Canadian setting were identified to be the hyper-CVAD or FLAG-Ida protocols followed by stem cell transplant. With regards to the benefit of blinatumomab, input indicated that this novel agent has shown superiority over a variety of standard-of-care protocols and it is expected more patients will proceed to stem cell transplant due to treatment with blinatumomab. Input from registered clinicians also indicated that the toxicity profile of blinatumomab is expected to be more manageable for patients compared with chemotherapy, particularly following transplant. Clinician input also acknowledged the toxicity profile of blinatumomab is different from those observed with chemotherapy. It is expected that toxicities will be manageable with adherence to the management protocols provided by the manufacturer. pERC noted that jurisdictions will need to manage the training of staff on the management of toxicities during implementation of blinatumomab. pERC considered further input from registered clinicians related to costs of blinatumomab, which are expected to be better managed by administering treatment in the outpatient setting. Given the considerable challenges to implementing outpatient treatment, as outlined by the PAG, pERC agreed that most patients will likely be treated with blinatumomab as in-patients, at least in the induction/consolidation phases.

PATIENT-BASED VALUES

Values of patients with acute lymphoblastic leukemia: Symptom and disease control

pERC deliberated on patience advocacy group input and noted that patients experience various disease-related symptoms that have a large impact on their daily lives. Patients reported that extreme fatigue had the most impact on daily life. Additionally, fatigue, fever and night sweats, and weight loss were identified as common symptoms that ALL patients desire to control. Loss of physical and emotional intimacy was also a commonly experienced symptom of disease. Overall, disease-related symptoms were reported to have a large impact on patients' daily lives.

Caregivers surveyed expressed a negative emotional impact from a loved one's diagnosis. Caregivers report experiencing some degree of anxiety regarding diagnosis and treatment. Furthermore, caregivers often have various new time commitments associated with caring for their loved ones, can often feel lonely, and experience pessimistic emotional states that affect their health and personal lives.

In deliberating on patient input, pERC noted that disease and symptom control were important to patients. The results of the TOWER study align with these patient values as patients' QoL was maintained in the blinatumomab group while deterioration was reported in the chemotherapy group. However, pERC noted that SAEs and the incidence of cytokine release syndrome increased with blinatumomab.

Patient values on treatment: Management of treatment-related side effects

Input from patients indicated that the main treatments used are chemotherapy, targeted therapy, and allogeneic stem cell transplant. All patients reported having some variation of side effects associated with their treatments. Common side effects of the current treatments include pain, nausea and vomiting, fatigue, infections/non-cancer illness, and fertility and sexual side effects. Most treatment side effects were reported to be temporary and subsided once the body adjusts to therapy or when therapy is completed. As patients' treatments are sometimes administered directly into the spinal canal, the required lumbar punctures were reported by some patients as being the worst part of treatment. All respondents had some form of infection or non-cancer illness, which for some had lasting impacts. Patients reported no difficulty accessing treatment and more than two-thirds of patient respondents indicated the current treatment did a sufficient job of managing their cancer symptoms.

Patients expressed a desire to have the following symptoms controlled with blinatumomab treatment: fatigue, pain, bruising and/or bleeding, numbness and tingling, loss of appetite, fever and/or night sweats, lumps, and rashes/skin changes. Patients indicated a willingness to tolerate short-term side effects like nausea, diarrhea, edema, and loss of appetite, as opposed to more severe side effects such as pain, bruising, and bleeding. Among three patients with experience using blinatumomab, two reported having suffered no additional side effects from the treatment and one stated that they no longer had to take anti-nausea medicine during blinatumomab treatment.

Overall, pERC noted that management of side effects related to current therapies is important to patients. While the increased SAEs with blinatumomab do not align with their values, pERC agreed that an improvement in OS and maintenance of QoL are important outcomes to patients.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) performed a cost-effectiveness and cost-utility analysis comparing blinatumomab with currently available treatments for patients with Ph– relapsed/refractory B precursor ALL. The comparator comprised a salvage therapy with hyper-CVAD (combination chemotherapy). The submitted model was a four-state partitioned-survival model.

Basis of the economic model: Underestimated incremental cost due to drug administration

Key costs considered in the analysis include cost due to drug acquisition, in-patient administration of treatment, nurse visits for IV-bag change, salvage therapy, stem cell transplant, terminal care, wastage and post progression. Key clinical inputs included OS, initial response rate, event-free survival, and utilities, all based on results from the TOWER study and extrapolation over patients' lifetimes.

The Committee discussed the various implementation challenges in administering blinatumomab in the outpatient setting and agreed that many patients are likely to be treated as inpatients until jurisdictions develop greater experience with blinatumomab treatment. Based on the submitted model, patients are in hospital only for the first 12 days of cycles 1 and 2. pERC therefore agreed that the incremental cost of drug administration is substantially underestimated. pERC also agreed that the administration/health system costs were underestimated, since only the nurse visit to change patients' IV bags was incorporated into the model and this does not take into account the complex dose preparation and time requirement involved with changing a blinatumomab infusion bag. The cost of infusion pump, however, was incorporated into the model.

Drug costs: High drug costs, especially compared with salvage therapy

Blinatumomab costs $2,978.27 per 38.5 ug vial. At the recommended dosage of 9 ug/day for week 1 and subsequent cycles increased to 28 ug/day starting week 2 through week 4 of the first cycle and all further cycles for the entire four-week cycle, the daily cost of blinatumomab for cycle 1 is $1,701.86 and $47,652 per 28 days. For cycle 2 forward the daily cost of blinatumomab is $1,985.50 and $55,594 per 28-days.

Hyper-CVAD consists of multiple agents. Based on the Sunnybrook Hospital protocol and cost data from Quintile IMS Delta PA, the cost of hyper-CVAD is $225.60 per day and $6,316.72 per 28 days. In the submitted model, the submitter used the Princess Margaret Hospital protocol and cost information based on Sunnybrook, McKesson, and the Ontario Drug Benefit Formulary. The per-cycle cost of hyper-CVAD was

$1383.50 with one cycle lasting on average 18.9 days. Based on this the cost of hyper-CVAD was calculated to be $73.20 per-day and $2,049.63 per 28-day cycle.

Cost-effectiveness estimates: Extrapolation of OS benefit

The Committee deliberated on the cost-effectiveness of blinatumomab and concluded that blinatumomab is not cost-effective when compared with hyper-CVAD. The Committee noted that a number of clinical assumptions in the submitted model overestimated the long-term benefit anticipated with the use of blinatumomab. Namely, pERC noted that the use of a 50-year time horizon, extrapolation of survival benefit beyond the trial period, and choice of parametric model used to extrapolate long-term survival all had a substantial impact on the incremental cost-effectiveness ratio (ICER). pERC noted that survival data from the TOWER study was only available up to 24 months. The pCODR Clinical Guidance Panel suggested a 10-year time horizon would be more clinically plausible in this patient population. The manufacturer also chose a parametric model for estimating long-term survival based on predictions from a historical cohort. The EGP altered this by using a parametric model that had the best statistical fit to the TOWER study data. Lastly, the Kaplan–Meier curves for OS appear to show convergence of OS between treatment groups around 15 to 18 months. Given these data, there is uncertainty in the anticipated long-term benefit with blinatumomab. To account for this uncertainty, the EGP assumed similar OS benefit beyond the trial period (after 18 months). When these changes were made the ICER increased from $72,488 at the base-case estimate to nearly $1 million/QALY. Furthermore, pERC noted that the incremental cost of blinatumomab is likely underestimated due to the assumption that most treatments will be given in an outpatient setting and that only the cost of a nurse changing the blinatumomab infusion bag was incorporated for administration costs. Overall, pERC agreed that blinatumomab is not cost-effective and will require a substantial price reduction to manage the cost-effectiveness and uncertainty related to clinical effect estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Implementation will require considerable cost and human resources

The Committee discussed factors affecting the feasibility of implementing a reimbursement recommendation for blinatumomab. Input from the PAG highlighted various challenges to implementing blinatumomab. These included the requirement for considerable coordination of pharmacy and nursing staff training to prevent medication error, strict adherence and intensive staff training for the complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer, and monitoring and treatment of toxicities. These concerns are supported by input from registered clinicians, who indicated that the toxicities observed with blinatumomab are different from chemotherapy. Therefore strict adherence to the toxicity management protocols will be important to manage treatment-related toxicities, which were demonstrated to be increased based on the TOWER study.

The Committee discussed factors affecting the feasibility of implementing a reimbursement recommendation for blinatumomab. Various implementation and feasibility challenges were discussed, including, but not limited to, the requirement for considerable coordination of pharmacy and nursing staff training to prevent medication error for both inpatient and outpatient administration; the strict adherence and intensive staff training for the very complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer; and the required monitoring and treatment of toxicities. pERC further noted that blinatumomab preparation/administration, due to its complexity, may be limited to certain treatment centres with adequate resources (e.g. appropriate ambulatory infusion pump supply, adequate staffing). In addition, pERC noted that, for logistical reasons, many patients may be treated as inpatients beyond the initial cycles, and administration of blinatumomab on an outpatient basis requires coordination amongst inpatient and outpatient facilities, availability of on-call support for patients should the issues arise with the infusion pumps, as well as frequent patient visits to treatment centres to coordinate changing of blinatumomab infusion bags/proper programming of electronic infusion pumps. The complexity of blinatumomab was further discussed by pERC since a variety of concentrations/durations of stability are possible for blinatumomab preparations and it was noted that administration/preparation protocols for blinatumomab may be different amongst jurisdictions in order to accommodate local resources - some jurisdictions may adopt to supply blinatumomab every 96 hours while other jurisdictions may adopt different infusion durations (e.g. every 48 hours, 72 hours) all of which require different infusion rates depending upon the blinatumomab concentration in the prepared product. Potential differences in protocol could impact upon potential drug wastage, particularly in

centers that do not treat many patients and where vial sharing is not feasible. Based on these various challenges, pERC agreed that the implementation of blinatumomab will require considerably more expenditures and human resources than accounted for in the economic model provided by the submitter. pERC further agreed that the budget impact of blinatumomab will increase due to these various additional costs.

The Committee noted that a previous reimbursement recommendation was made for the use of blinatumomab in patients with Philadelphia chromosome–negative relapsed/refractory B precursor ALL and who have had at least two prior lines of systemic therapy. Based on the evidence presented in the TOWER trial, pERC agreed that blinatumomab will likely be moved up to be used at first relapse. This is in agreement with input from registered clinicians, who indicated that the best available therapies should be used earlier in a patient's treatment course. However, pERC acknowledged that there will be a short time-limited need for blinatumomab in patients who have had two prior lines of systemic therapy.

DRUG AND CONDITION INFORMATION

Drug Information	• First-in-class bispecific T-Cell engaging (BiTE) antibody construct • 38.5 mcg/vial • Recommended dosage of 9 ug/day for week 1 escalated to 28 ug/day for three weeks, followed by two-week treatment-free interval, and then up to four subsequent cycles of 28 ug/day for four weeks (each followed by a two-week treatment-free interval)
Cancer Treated	• Philadelphia chromosome-negative relapsed/refractory B precursor acute lymphoblastic leukemia
Burden of Illness	• 15% of adult cases of acute leukemia • Significant symptom burden on patients and quality of life impact • Prognosis of patients is poor and prolonged survival is vanishingly rare
Current Standard Treatment	• Salvage combination chemotherapy (e.g., hyper-CVAD or any chemotherapy not used in upfront therapy) followed by allogeneic hematopoietic stem cell transplant where possible
Limitations of Current Therapy	• Limited impact on long-term prognosis of patients as most patients eventually die of their disease.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Jo Nanson, who was not present for the meeting.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of blinatumomab (Blincyto) for adult acute lymphoblastic leukemia (ALL) through their declarations, four members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC base its recommendations on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

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