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PAN-CANADIAN
ONCOLOGY DRUG REVIEW

**pan-Canadian Oncology Drug Review
Final Economic Guidance Report**

**Blinatumomab (Blincyto) for Pediatric Acute
Lymphoblastic Leukemia**

August 23, 2017

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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This section outlines the technical details of the pCODR Economic Guidance Panel’s evaluation of the economic evidence that is summarized in Section 1. Pursuant to the <i>pCODR Disclosure of Information Guidelines</i> , this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.	
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Amgen Canada compared blinatumomab to standard of care for pediatric patients with relapsed/refractory (R/R) Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL).

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Funding request matches patient population modeled and that of the phase I/II clinical trial. Relapsed/refractory disease was defined according to the Study MT103-205 trial, as follows: <ul style="list-style-type: none"> • Refractory to other treatments; <ul style="list-style-type: none"> o Patients in first relapse must have failed to achieve a CR following full standard reinduction chemotherapy regimen of at least 4 weeks duration o Patients who have not achieved a first remission must have failed a full standard induction regimen • Any marrow relapse after allogeneic HSCT; or • Second or later bone marrow relapse
Type of Analysis	CUA & CEA
Type of Model	Partitioned-survival model
Comparator	Based on the CGP input, there is no single accepted standard of care for this patient population. For the purposes of the economic evaluation, a historical comparator, study 20140228 (standard of care consisting of salvage multi-drug chemotherapy) was used
Year of costs	2016
Time Horizon	Lifetime (95 years)
Perspective	Canadian health care payer
Cost of blinatumomab	<ul style="list-style-type: none"> • The unit cost of blinatumomab is \$2,978.26 per 38.5 mcg of lyophilized powder in a single-use vial for reconstitution. • In the MT103-205 trial, on average, subjects initiated two cycles of blinatumomab, and consumed 1.4 cycles, which corresponds to 39 vials (assuming one vial per day on blinatumomab treatment). The cost of 39 vials is \$116,152. <p>The cost of blinatumomab per 28-day course is \$55,594.20 (This includes 4 weeks of continuous IV infusion. Each cycle of treatment is separated by a two week treatment-free interval).</p>

<p>Cost of standard of care consisting of salvage multi-drug chemotherapy[#] <i>Price Source: IMS Brogan accessed June 19, 2017.</i></p>	<p>There is no standard of care (SOC) for pediatric patients with relapsed/refractory Ph- ALL.</p> <p>The SOC consists of salvage multi-drug chemotherapy. Based on cost data from Quintiles IMS Delta PA, the cost for initial induction and two consolidation blocks are as follows:</p> <ul style="list-style-type: none"> • UK R3 ALL: \$6,469.81 • COG-AALL 1331: \$15,605.91 • COG-AALL 0031: \$11,004.95 <p>Based on cost data from Quintiles IMS Delta PA, the cost of clofarabine is \$128.96 per mg or \$31,852.01 per phase.[^]</p> <p>In the submitted model, the unit costs of each component of the chemotherapy regimens were based on cost data from McKesson Canada and the Ontario Drug Benefit Formulary, as well as Canadian distributors and manufacturers. The average cost for the combined therapies was \$11,246.</p> <ul style="list-style-type: none"> • The cost for initial induction and two consolidation blocks are as follows: • UK R3 ALL: \$13,678.73 • COG-AALL 1331: \$16,371.77 • COG-AALL 0031: \$3,686.60 <p>The cost of clofarabine was not included in the submitted base case. Based on the manufacturer of clofarabine, the total cost of clofarabine is \$128.96 per mg or \$31,885.54 per phase.[~]</p>
<p>Model Structure</p>	<p><i>Three distinct health states included: remission (complete remission), progressive disease (includes progressive disease, aplastic bone marrow or partial remission), and death. Patients who survive for 60 months in the treatment phase were assumed to be cured.</i></p>
<p>Key Data Sources</p>	<p><i>Study MT103-205 (phase 1 & phase 2) to inform intervention arm</i> <i>Study 20140228 to inform comparator arm</i> <ul style="list-style-type: none"> o <i>NOTE: there is no RCT to inform this economic model</i> </p>
<p>Notes: [#]Cost for one cycle for a pediatric patient at 8 years of age with a body surface area of 0.95.; [^] 52 mg/m² x 5 doses.; [~] Based on the recommended dose of clofarabine (52 mg/kg); ⁺ Costs are calculated based on patients weighing > 45 kg (fixed dose). Dosage for patients weighing < 45 kg is based on body surface area.</p>	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, given the absence of phase III data. The CGP noted that historical comparisons are not ideal. The CGP noted that a phase 3 randomized controlled trial is currently underway and will provide evidence on the role of blinatumomab in first line relapsed pediatric ALL.

Relevant issues identified included:

- There may be a net clinical benefit.
- Interpretation of non-comparative results using historical controls should be interpreted with caution.
- There is no data on the impact of blinatumomab on the quality of life of pediatric ALL patients.
- Although patients may be able to receive blinatumomab in the outpatient setting, the supportive care and pharmacy requirements for pediatric patients with relapsed/refractory ALL who are receiving blinatumomab would likely require pediatric patients to remain in close proximity of the hospital due to the support required during the course of therapy (e.g. transfusion support, portable infusion pump, nursing care for pump maintenance). Further, pediatric centres that do not have the appropriate outpatient resources to administer and monitor blinatumomab will require patients to be treated as an inpatient beyond the initial cycle of therapy.

Summary of registered clinician input relevant to the economic analysis

Registered clinicians supported the use of multi-drug chemotherapy and clofarabine-based regimens as appropriate comparators for this population. Additionally, alloHSCT, off study compassionate access to therapy or experimental therapy in a clinical trial setting were noted as options for relapsed/refractory pediatric patients. Registered clinicians stated that there are very few (if any) long term toxicities associated with blinatumomab compared to chemotherapy. There is, however, the possibility of short term neurotoxicity that can be severe. Registered clinicians also felt that blinatumomab is also at least as effective as conventional chemotherapy for this patient population.

Summary of patient input relevant to the economic analysis

Patients, via their caregivers, considered the side of effects of treatments as an important consideration; adverse events were not incorporated into the model. Caregivers of patients also considered the societal costs of the disease as important; these were not considered as the economic model was constructed from the government payer perspective. Patients/caregivers are seeking treatment to achieve disease remission and to stop disease progression; overall survival and time in remission were considered in the economic model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors important to consider if implementing a funding recommendation for blinatumomab which are relevant to the economic analysis:

Enablers

- New class of drug that fills gap in therapy for pediatric relapsed/refractory ALL.
- Barriers
- Unusual dosing schedule of 28-day continuous infusion with 2 weeks off.

- Resource intensive preparation and administration (e.g. different infusion durations per preparation bag [between 24-96 hours], different pump infusion rates with different durations of infusion, etc.).
- High rate of toxicities, particularly neurotoxicities, to monitor and treat.
- Hospitalization for administration of blinatumomab for the first cycle and for the first two days of the second cycle; proximity to tertiary care centres required.
- High cost of drug.
- Pre-medications required prior to first dose of each cycle.
- Multiple clinic visits for infusion bag to be changed and multiple visits required to prepare infusion bags during the four week infusion period.
- Drug wastage would be an issue as there is only one vial size of blinatumomab, and dosages are much smaller for pediatric patients (e.g., patients who weigh less than 45 kg).
- Since the stability of the reconstituted vials is 24 hours refrigerated and the stability of the prepared infusion bags is 10 days refrigerated, one vial can be used to prepare more than one infusion bag. However, 5.5mL of stabilizer is required to prepare each infusion bag and there is only 10mL of stabilizer included with each vial of drug. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. Therefore, wastage is a concern where partial vials may be used as the amount of stabilizer available within each package of blinatumomab is only sufficient for one infusion preparation.
- Portable, programmable, lockable infusion pumps used to administer blinatumomab in the outpatient setting may not be readily available in all treatment centres.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	4.98	8.64	1.30
Remission	0.85	1.47	0.24
Progressive disease	-0.05	-0.08	-0.03
Cure (after 5 years)	4.19	7.25	1.08
ΔE (QALY)	4.26	7.38	1.11
Remission	0.68	1.18	0.20
Progressive disease	-0.02	-0.03	-0.01
Cure (after 5 years)	3.60	6.23	0.93
ΔC (\$)	\$67,913	\$48,572	\$112,363
ICER estimate (\$/QALY)	\$15,940	\$6,577	\$100,948

The main assumptions and limitations with the submitted economic evaluation were:

- The main limitation of this economic model is the lack of comparative effectiveness data and the resulting uncertainty in relative efficacy between the two treatment arms. The three comparators chosen were from a historical comparator. Age was not used as a strata to adjust between the two comparator arms. The CGP indicated that age is an important effect modifier for pediatric ALL. Further, one of the regimens considered in the historical comparator (COG-AALL 0031) is not considered appropriate by the CGP.
- Small sample size for efficacy data for blinatumomab, which may lead to bias in generalizability.

- Quality of data in the historical comparator due to variables missing not at random for duration of response. This implies that the value of the variable that is missing is related to the reason it is missing.
- Uncertainty around duration of treatment for blinatumomab.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Time horizon: The economic model assumes that patients enter at 8 years of age and are “cured” if they are alive at 60 months. The base case then assumes a time horizon of 95 years from this point. The EGP elected to reduce the time horizon to 70 years (from cure), as these patients will most likely have late effects from chemotherapy, increasing their morbidity and most likely the mortality when adults (compared to the general population). The likelihood of any person in the general Canadian population living to 108 years old is very unlikely (as in the submitted base case).
- Comparator: The submitter assumed in the base case an equal split (i.e., 1/3) between UK R3 ALL, COG-AALL 1331 and COG-AALL 0031 regimens, excluding clofarabine. The CGP indicated that although clofarabine is not a first choice among clinicians due to the associated toxicities, it is a possible comparator. Further, the CGP indicated that COG-AALL 0031 regimen is not a likely choice in the relapsed/refractory setting. The EGP, based on the feedback from the CGP, made changes to the comparator to include clofarabine (33%), and exclude COG-AALL 0031 as part of the reanalysis.
- Overall survival hazard ratio: Given the lack of comparative effectiveness data, and the limitations noted in the chosen comparators and data used, the EGP elected to examine the uncertainty of overall survival by using the lower and upper bound of overall survival in the reanalysis estimates.
- Hospital length of stay during treatment with blinatumomab: The CGP noted that not all centres will have access to portable infusion pumps for their patients. In order to examine a conservative estimate, the EGP examined as an upper bound a scenario where patients receive blinatumomab only in a hospital setting, which translates to a length of stay of 60 days in hospital (instead of base case of 30 days in hospital, with the remainder using a portable infusion pump in the outpatient setting).

Table 3. EGP Reanalysis Estimates

	ΔC	ΔE QALYs	ICUR (QALY)	
Baseline	\$67,913	4.26	\$15,940	-----
EGP's Reanalysis for the Best Case Estimate - Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
<i>Time horizon - 70 years (from cure)</i>	\$67,822	4.14	\$16,396	\$456
<i>Overall survival - lower 95% CI</i>	\$68,739	7.61	\$9,036	-\$6,904
<i>Comparator composition: 33% R3, 33% 1331, 33% clofarabine</i>	\$47,885	4.26	\$11,239	-\$4,701
Lower bound best case estimate - modification of all above parameters	\$48,572	7.38	\$6,577	-\$9,363
EGP's Reanalysis for the Best Case Estimate - Upper Bound				
<i>Time horizon - 70 years (from cure)</i>	\$67,822	4.14	\$16,396	\$456
<i>Overall survival - upper 95% CI</i>	\$67,141	1.15	\$58,581	\$42,641

Hospital length of stay blinatumomab - 60 days	\$113,183	4.26	\$26,566	\$10,626
Upper bound best case estimate - modification of all above parameters	\$112,363	1.11	\$100,948	

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the treatment duration (i.e. the number of vials of blinatumomab to be used). Increasing the number of vials to 45, from 39, increases the incremental three-year costs.

Key limitations of the BIA model include the lack of inclusion of drug administration costs, which could be significant for blinatumomab. However, these administration costs may not be more incrementally expensive than current standard of care chemotherapy. This parameter was not able to be modified and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for blinatumomab when compared to the standard of care given the submitted model is:

- Between \$6,577/QALY and \$100,948/QALY
- The extra cost of blinatumomab is between \$48,572 and \$112,363. *The factors that most influence ΔC are the hospital length of stay for either blinatumomab or the standard of care, the cost per day for an inpatient stay, the number of vials of blinatumomab consumed and the choice of composition of the comparator.*
- The extra clinical effect of blinatumomab is between 1.11 and 7.38 (ΔE). *The factors that influence ΔE are the hazard ratio for overall survival and the utility for long-term survival.*
- *The CGP noted that the estimates of comparative efficacy derived from the comparison of the single arm MT103-205 trial with historical data should be interpreted with extreme caution. The comparison with a historical comparator is the best current available data for this limited population.*
- *Additionally, the EGP was not able to modify various important model parameters that were noted to potentially have an impact on the clinical effectiveness estimates.*

Overall conclusions of the submitted model:

- *Though the submitted model is fully functional and captures the majority of key inputs, there is too much uncertainty in the comparative effectiveness that cannot be captured in the reanalysis. For example, if there was no overall survival benefit between blinatumomab and the historical comparator, the ICER approaches \$9 million.*
- *The use of a historical comparator limited the data available for the economic model. However, due to challenges in performing clinical trials in the pediatric population, the EGP performed reanalysis estimates despite the numerous limitations of assumptions in the economic model.*
- *This pediatric economic model has the potential for relatively large magnitude of gains for effects (submitted base case = 4.26 QALYs), given that ALL can be cured and a pediatric patient could continue to live for more than 60 years beyond cure.*
- *The large gains in efficacy translate into a relatively lower submitted base case ICER. The EGP cautions that the upper bound of the reanalysis estimate may exceed that provided in this report.*
- *Information from direct comparative trials with longer follow-up is still warranted.*

2 DETAILED TECHNICAL REPORT

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3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR pediatric Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of blinatumomab (Blincyto) for relapsed/refractory Philadelphia negative pediatric ALL. A full assessment of the clinical evidence of blinatumomab (Blincyto) for relapsed/refractory Philadelphia negative pediatric ALL is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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