CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Blinatumomab (Blincyto) Resubmission for Acute Lymphoblastic Leukemia

August 31, 2017

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Amgen** compared blinatumomab to Hyper-CVAD for patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (R/R Ph(-) ALL).

Table 1. Submitted Economic Model

Table 1. Submitted Economic Model	
The funding request was for blinatumomab for all refractory or relapsing patients with B-precursor Philadelphia chromosome negative [Ph-] acute lymphoblastic leukemia	The economic model was based on the comparators and evidence from the TOWER study. The TOWER study compared blinatumomab with investigators choice of chemotherapy in patients with Philadelphia chromosome (Ph)-negative B-precursor ALL who were refractory to or relapsed on previous therapy.
Type of Analysis	Cost Utility Analysis
Type of Model	4 health state partitioned survival model
Comparator	Blinatumomab vs. chemotherapy Hyper-CVAD was assumed to be the chemotherapy that blinatumomab was being compared to. This was assumed for costing purposes only. Clinical data was based on all chemotherapies given in the TOWER study, Hyper-CVAD was chosen because it is the most common chemotherapy given to this patient group in Canada. Note that no patients in the TOWER study received hyper-CVAD.
Year of costs	*2016*
Time Horizon	*50 years*
Annual Discount Rate applied	*1.5%*
Perspective	*Government*
Cost of blinatumomab	Blinatumomab costs $2,978.26 per 38.5ug vial • Recommended dose in cycle 1 is 9ug/day for week 1 (first 7 days). • Subsequent cycles increased to 28ug/day starting week 2 through week 4 of first cycle. All subsequent cycles also dosed at 28ug/day through entire 4 week cycle. At the recommended dose and based on the TOWER protocol, blinatumomab costs: • $47,652 per 28-days (cycle 1) • $55,594 per 28-days (cycle 2+) When cost calculations are based on 6 week cycles (42 days), blinatumomab costs: • $71,478 per 42-day cycle (cycle 1) • $83,391 per 42-day cycle (cycle 2+)

Table 1. Submitted Economic Model	
	*assumes that 3 vials can be shared and will be used for days 1-7 of cycle 1 and that one 38.5ug vial will be used for all other treatment days
Cost of chemotherapy[#]	Hyper CVAD consists of multiple agents. Based the Sunnybrook Hospital protocol and cost data from Quintile IMS Delta PA, the cost of Hyper-CVAD is $225.60 per day and $6316.72 per 28 days In the submitted model, the submitter use the Princess Margaret Hospital protocol and cost information based on Sunnybrook, McKesson and ODBF. The cost of Hyper-CVAD to be $73.20 per day and $2049.63 per 28 day cycle[&]. The exact number of treatment days per cycle was not specified. Based on OCCI data, the model assumed that a course of hyper-CVAD would require on average 18.9 days of treatment
Model Structure	The model was comprised of 4 health states: 1) Initial treatment; 2) Response; 3) Relapsed/Refractory; 4) Dead The following determine the proportion of patient that are in each of the health states every cycle. • Initial response rates (12 weeks) • Event Free survival amongst responders • Overall survival
Key Data Sources	TOWER Study, a phase 3 RCT trial which compared blinatumomab to chemotherapy in refractory or relapsing patients with B-precursor [Ph-] ALL was used to estimate: • Initial response rates (12 weeks) • Event Free survival amongst responders • Overall survival • Utility values • Subsequent treatments • Proportion of patients with allogenic stem cell transplant
Foot Notes: All cost calculations for IV drugs are based on a BSA=1.7m^2; weight = 70kg *Acronyms: Hyper: hyper fractionated; CVAD: Course A-cyclophosphamide, doxorubicin, vincristine, dexamethasone + Course B - methotrexate, cytarabine as per Sunnybrook Hospital protocol; OCCI: Ontario Case Costing Initiative; OBDF: Ontario Drug Benefit Formulary* **Cost calculations for blinatumomab based on a combination of 24, 72 and 96 hour infusion which minimize wastage.* [#]Price Soucre: Quintile IMS Delta PA accessed on June 5, 2017 [&] The per-day and 28-day cost of hyper-CVAD was calculated as follows. In the Submitted model hyper-CVAD costs $1383.50 per cycle. Given that a cycle was reported to be 18.9 days, $1383.50/18.9= $73.20 per day and $2049.63 per 28-days.	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. Relevant issues identified included:

- *In the TOWER study, blinatumomab was compared to one of 4 chemotherapy regimens FLAG, high dose Ara or High dose methotrexate based regimes or clofarabine. Although none of these options included a comparator most often used in the Canadian setting (Hyper-CVAD), the CGP agreed that the overall trial results are generalizable to the Canadian clinical setting.*
- Blinatumomab provides a net clinical benefit to patients. Based on the Kaplan-Meir curves for overall survival by about month 16 of treatment, the blinatumomab and chemotherapy arms converge. The CGP agreed that the benefit of blinatumomab appears to be within the first couple months of treatment where the prolonged survival may provide patients with greater opportunity to get to transplant.
- Blinatumomab cannot be considered a curative treatment but more as a bridge to other salvage treatments such as allogeneic HSCT. CGP came to this conclusion as the outcomes for refractory patients and those relapsing post HSCT receiving conventional chemotherapy or blinatumomab are very similar.

Summary of registered clinician input relevant to the economic analysis

There were a number of points identified through registered clinical input that are relevant to the economic analysis. These included the following:

- Even though Blinatumomab is a high cost drug, it can be administered an outpatient basis. This would significantly reduce the cost of hospitalization**.** This is addressed in the economic analysis as it incorporates the costs of both inpatient and outpatient treatment administration.

- Blinatumomab has less infectious side effects, which should also save on costs of managing side effects.
  This is not addressed in the economic evaluation as the cost impact of adverse events are not incorporated.

Summary of patient advisory group input relevant to the economic analysis

The patients advisory group noted that all caregivers "suffer a degree of loss of work due to their love one' diagnosis". Indirect costs such as work productivity loss costs for patients and caregivers are not addressed in the economic evaluation. Patients also experience many disruptions to their life due to treatment related side effects. Cost and quality of life impacts of adverse events are not captured in the model.

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

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

- PAG stated concerns that access to blinatumomab would be limited to treatment centers with appropriate resources to coordinate inpatient care and outpatient clinics. *This issue is not addressed in the economic analysis*.
- PAG noted that the preparation, administration and monitoring of blinatumomab is very resource intensive. They note following concerns:
  - 28 day continuous infusion, requiring coordination of resources to change infusion bags
    The economic analysis does not address this issue.

- Hospitalization for administration for the first nine days of the first cycle and the first two days of the second cycle
  The economic analysis does address this. The submitted model assumed that patients receiving blinatumomab would be hospitalised during the first 12 days of Cycle 1 and also conservatively for the first 12 days of Cycle 2. This was considered to be a conservative assumption given that hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. All subsequent cycles would be received on an outpatient basis with daily IV bag changes by a clinical nurse.
- Pre-medication with intravenous dexamethasone prior to first dose of each cycle and whenever infusion is interrupted for more than four hours
  The economic analysis does not address this issue.
- Significant pharmacy and nursing staff training to prevent medication error.
  The economic analysis does not address this issue.
- Strict adherence and intensive staff training for the very complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer
  The economic analysis does not address this issue.
- Monitoring and treatment of toxicities, particularly neurotoxicities with 50% incidence and 15% at grade 3 or higher
  The economic analysis does not address this issue.
- PAG noted that drug wastage is minimized with the 96 hour stability of infusion solution.
  - In the economic model it is assumed that 3 vials of blinatumomab can be shared during the first 7 days of treatment. Afterwards it is assumed that 1 full vial would be used per treatment day

- PAG identified the high cost of the drug, the one vial size and lack of long term data being barriers to implementation. The submitted economic analysis does include the cost of blinatumomab in the analysis. The submitted economic analysis addresses the lack of long term data by using statistical modelling techniques to extrapolate the short term trial data. The economic analysis assumed after the first seven days, that 1 full vial of blinatumomab would be used per infusion.

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers of the manufacturers' model were drug acquisition costs and drug administration costs. Other inputs to the model that affected estimates of costs were subsequent treatment costs and costs of stem cell transplant.

The main drivers of the clinical outcomes of the model (QALYs, Life Years) were: 1) overall survival estimates; 2) 12 week response rates; 3) event free survival amongst responders; 3) the time horizon used in the model and 4) the utility values assigned to patients over the duration of the model time horizon. Overall the approach taken in the economic evaluation was reasonable and appropriate.

Table [2]. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis	
		Lower Estimate	Upper Estimate
ΔE (LY)	2.54	0.81	0.14
Progression-free (initial and response health states)	0.49	0.38	0.39
Post-progression (refractory/relapse health state)	2.04	0.43	-0.25
ΔE (QALY)	2.18	0.71	0.16

Progression-free (initial and response health states)	0.42	0.33	0.33
Post-progression (refractory/relapse health state)	1.76	0.38	-0.17
ΔC ($)	$158,183	$158,224	$158,270
ICER estimate ($/QALY)	$72,488	$223,060	$971,327

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

- Time Horizon: The model uses a 50 year time horizon. Using such a long time horizon can lead to erroneous predictions of long term survival based on extrapolation of trial data with limited follow-up. While the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (Page 43). Survival data from the TOWER study amongst patients with no previous salvage therapy was only available up to 24 months. The CGP suggested using a 10 year time horizon was more clinically plausible in this patient population. This 10 year time horizon was assumed by the EGP in the re-analysis. Furthermore, in a previous submission for the same patient group the EGP also assumed a 10 year time horizon in their re-analysis.

- Statistical model for overall survival: The choice of statistical model to extrapolate overall survival can have a big impact on model results. The manufacturer's choice of a Gompertz model for overall survival was largely based on the plausibility of long term predictions compared to an historical cohort. However, the log-logistic model had the best statistical fit to the TOWER study data. In the EGP reanalysis the log-logistic model was used to estimate overall survival because of the better statistical fit.

- Convergence of overall survival: The Kaplan-Meier curves for overall survival appear to show convergence of OS between treatment groups around 15 to 18 months. There is some separation between curves between months 18 and 24 due to a large drop in survival in the SOC curve at that time. However there are only 4 patients at risk in the SOC arm after 18 months, making it likely that the separation is due to a single death in the SOC arm between 18 and 24 months. The CGP noted the convergence of survival curves in the clinical report as well. This raises questions about whether it is appropriate to project differences in overall survival between treatment groups after 18 months. Therefore, in the EGP reanalysis overall survival for blinatumomab is assumed to be the same as overall survival for standard of care after 18 months.

- Adverse Events: The cost and quality of life impact of adverse events were not incorporated into the model. This is not addressed in the EGP reanalysis. The submitter stated in the PE report that "the costs of AEs were not considered explicitly in the model but were assumed to be captured in the costs of inpatient and outpatient care for the administration of blinatumomab and SOC chemotherapy."

- Cost of Hyper-CVAD: Based on cost acquired through the Quintile IMS Delta PA database, the cost of Hyper-CVAD is substantially different from what was used in the submitted model (nearly 80% price reduction in Hyper-CVAD). While the confidential cost of the Hyper-CVAD regimen is unknown, it is likely to be substantially lower than the cost presented in the Quintile IMS Delta PA database. The base case results and EGP reanalysis estimates are based on the cost used in the economic model. As the confidential price of Hyper-CVAD is likely to be lower than what is used in the economic model, the ICER's presented may be underestimating the incremental cost difference between Hyper-CVAD and blinatumomab.

1.4 Detailed Highlights of the EGP Reanalysis

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

- The time horizon of the model was 50 years. The CGP agreed this was not appropriate for the patient population under review. The EGP reduced the time horizon to 10 years. This is consistent with the previous review for blinatumomab in this population.
- The overall survival curve used in the Submitted model was based on the Gomprtz distribution which the EGP agreed did not fit the observed trial data best. The EGP instead used the log-logistic distribution
- Based on the TOWER study, the overall survival curves for the blinatumomab group and the chemotherapy group converge around 15 to 18 months. Given the absence of data to support long term OS benefit in favour of the blinatumomab group, the EGP set overall survival for the two treatment groups to be equal after 18 months.
- The results of the EGP reanalyses are provided in Table 3. A sensitivity analysis assuming reductions on the acquisition costs for blinatumomab (25%, 50%, 75%) is shown in Table 4.

Table 3. Detailed Description of EGP Reanalysis

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Submitter's Basecase	$158,183	2.182	$72,488	-----
2. Change time horizon from 50 years to 10 years	$158,224	0.709	$223,060	$150,572
3. Change distribution used for overall survival to log-logistic	$158,827	0.456	$348,092	$275,604
4.Assume same overall survival after 18 months	$157,738	0.168	$938,894	$866,405
Lower estimate of cost effectiveness (includes changes in 2)	**$158,224**	**0.709**	**$223,060**	**$150,572**
Upper estimate of cost effectiveness (includes changes in 2,3,and 4)	**$158,270**	**0.163**	**$971,327**	**$898,838**

Table 4. Sensitivity analysis on EGP reanalysis assuming discounted cost of blinatumomab

	$/QALY by blinatumomab acquisition cost discount %			
Description of Reanalysis	**0%**	**25%**	**50%**	**75%**
1. Submitter's Basecase	$72,488	$53,498	$34,508	$15,518
2. Change time horizon from 50 years to 10 years	$223,060	$164,635	$106,210	$47,786
3. Change distribution used for overall survival to log-logistic	$348,092	$257,264	$166,435	$75,607
4.Assume same overall survival after 18 months	$938,894	$692,246	$445,599	$198,952
Lower estimate of cost effectiveness (includes changes in 2)	**$223,060**	**$164,635**	**$106,210**	**$47,786**
Upper estimate of cost effectiveness (includes changes in 2,3,and 4)	**$971,327**	**$716,972**	**$462,617**	**$208,262**

1.5 Evaluation of Submitted Budget Impact Analysis

The overall approach and of the BIA appears to be reasonable and appropriate. The factors that most influence the BIA are the estimated number of patients eligible for blinatumomab in the next three years, the assumed proportion of eligible patients that would be prescribed blinatumomab if it was reimbursed and the cost of blinatumomab and alternative treatments. A key limitation of the BIA is that it did not include the costs of administering the medication. Additionally, there were some simplified assumptions in the model. Only hyper-CVAD was considered as an alternative treatment in the BIA. Additionally, it was assumed that 100% of patients would be switched to blinatumomab under the scenario that it would be reimbursed. It is difficult to assess the impact of only considering hyper-CVAD as an alternative treatment without knowing the costs of other alternative treatments. Assuming 100% market share for blinatumomab, should it be reimbursed, should result in the most conservative (high estimate) of budget impact. The BIA was taken from a Canada wide perspective.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for blinatumomab when compared to Hyper-CVAD is:

- Between $223,060 /QALY and $971,327/QALY
- The extra cost of blinatumomab is between 158,224 and $158,270. Incremental costs were most impacted by drug acquisition costs.
- The extra clinical effect of blinatumomab is between 0.163 to 0.709 ΔE. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Overall conclusions of the submitted model:
The overall structure and data sources of the economic model were appropriate. However there is a lot of uncertainty surrounding the projections of overall survival benefit of blinatumomab over the model's 50 year time horizon. The TOWER study, from which survival benefits are extrapolated had less than 2 years of follow up data. The projections of incremental survival were very sensitive to the specific survival model chosen. Additionally, the Kaplan Meier overall survival curves for the two treatment groups completely converge from 15 to 18 months. This puts into question whether a survival benefit, in favour of the blinatumomab group, is plausible beyond 18 months.

The EGP's responses to the submitter's feedback on the initial economic guidance report:

The submitter raised concerns over the CGP and EGP recommendation of using a 10 year time horizon for the model. The submitter stated that their base case assumption of a lifelong time horizon was appropriate and consistent with CADTH recommendations. The EGP acknowledges that while the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (Page 43). Survival data from the TOWER study amongst patients with no previous salvage therapy was only available up to 24 months. The CGP suggested using a 10 year time horizon was more clinically plausible in this patient population. The EGP continues to believe that a 10 year time horizon is appropriate.

The submitter did not agree with the EGP re-analysis of assuming no survival benefit for blinatumomab compared to placebo beyond 18 months. The submitter stated their belief that blinatumomab provides a long term survival benefit compared to placebo and that caution should be given to the tail end of the KM curves due to the low number of patients at risk and the

confounding effects of allogenic stem-cell treatment and treatment switching. The CGP and EGP agree that there is much uncertainty on the overall survival benefit of blinatumomab beyond 15 to 18 months. Furthermore both the EGP and CGP agree that a conservative approach to the long survival benefit beyond the trial is warranted. This includes a scenario analysis in the EGP re-analysis in which no survival benefit is assumed after 18 months. In the EGP lower cost-effectiveness estimate, survival convergence after 18 months is not assumed.

The submitter did not agree with the EGP using the log-logistic model to project overall survival in their reanalysis of the model. The submitter noted that EGP based this decision solely on the criterion of model statistical fit. The submitter noted their choice of a Gompertz distribution was based on a combination of visual inspection, clinical plausibility and statistical fit which is consistent with the CADTH Guidelines. The EGP agrees that visual inspection and clinical plausibility should be considered in addition to statistical fit when choosing amongst statistical models. However weighing these components is somewhat subjective. As shown in the re-analysis, the choice of model can have a big impact on results. It should be noted that the EGP's lower bound cost-effectiveness estimate, the submitters OS model (Gompertz) is assumed. In the EGP upper bound cost-effectiveness estimate the choice of model has little impact as no survival benefit assumed after 18 months. The EGP believes it is appropriate to use the log-logistic model for overall survival in their re-analysis.

Furthermore, the EGP noted feedback from PAG requesting input on where the true ICER may lie closer to the upper or lower range of the re-analysis estimates. The EGP reiterated that the biggest impact on the ICER is uncertainty in long term overall survival. Without the availability of longer term overall survival data, the EGP is unable to provide further guidance on where the true ICER may be.

2 DETAILED TECHNICAL REPORT

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 *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR 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 acute lymphoblastic leukemia (ALL). A full assessment of the clinical evidence of blinatumomab (Blincyto) for acute lymphoblastic leukemia (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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.

REFERENCES

pan-Canadian Oncology Drug Review Manufacturer Submission: Blinatumomab (Blincyto) 38.5gu vial; Company: Amgen. Mississauga (ON): Amgen; 2017 Feb 24.

Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017 Mar 2;376(9):836-47.

Amgen response to pCODR checkpoint meeting questions on blinatumomab (Blincyto) for acute lymphoblastic leukemia [additional manufacturer's information]. Mississauga, (ON): Amgen; 2017 Apr 4.