

## 5.03 BLINATUMOMAB powder for IV infusion, 38.5 µg, Blincyto®, Amgen.

### 1 Purpose of Application

- 1.1 The submission requested a Section 100, Highly Specialised Drug Program listing for blinatumomab for the treatment of relapsed or refractory Philadelphia negative (Ph-) B-precursor acute lymphoblastic leukaemia (ALL).

### 2 Requested listing

Secretariat suggested wording for the restriction has not been presented at this stage due to the clarifications required in the proposed PBS listing.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Ex-manufacturer price/vial	Proprietary Name and Manufacturer	
<b>Initial treatment</b>					
BLINATUMOMAB Lyophilised powder in a single-use vial for IV infusion, 38.5 µg	up to 28 vials <sup>a</sup>	0	\$ [REDACTED]	Blincyto®	Amgen
<b>First and second continuing treatment</b>					
BLINATUMOMAB Lyophilised powder in a single-use vial for IV infusion, 38.5 µg	28	0	\$ [REDACTED]	Blincyto®	Amgen

#### **Section 100 – HSD Authority required (Public/private hospital)**

Treatment for adult patients with relapsed or refractory Philadelphia negative B-cell acute lymphoblastic leukaemia

<sup>a</sup> To be determined based on advice from PBAC and other relevant stakeholders. The dispensed price for maximum quantity to be determined once maximum quantities are agreed for each listing.

- 2.1 The submission proposed that blinatumomab would be provided as an inpatient and as an outpatient. In the first cycle, patients should be an inpatient for at least nine days, and for the second cycle, for at least two days. This is due to the risk of uncommon neurologic events, which have a median onset time of nine days, and cytokine release syndrome, which has a median onset time of two days. The submission considered that it would follow the precedence of eculizumab for the treatment of atypical haemolytic uraemic syndrome, the only PBS item which is also provided to inpatients.
- 2.2 The submission used three arguments to support their case for requesting funding in the inpatient hospital setting.
- Relapsed or refractory ALL patients are either hospitalised when therapy is commenced or are admitted to hospital for initiation of treatment.
  - The high cost of blinatumomab means that treatment according to the submission would be highly unlikely to be funded by the hospitals.
  - The current mechanisms and/or framework for provision of high cost PBS reimbursed chemotherapy through the outpatient setting would not be practical with blinatumomab nor would it provide quality use of medicine. According to the submission, monitoring for toxicities over the initial treatment periods should be conducted continuously.

- 2.3 While eculizumab for atypical haemolytic uraemic syndrome (aHUS) is subsidised in the inpatient setting (Public Summary Document July 2014), infliximab for the treatment of patients with acute ulcerative colitis (Public Summary Document, November 2013) is not subsidised in the inpatient setting, even though treatment is provided to inpatients in the first cycle. Both examples could be relevant for the consideration of whether blinatumomab should be provided in the inpatient setting. The Pre-Sub-Committee Response (PSCR, p1) argues that whilst infliximab is for admitted patients, acute ulcerative colitis is a non-fatal disease and that relapsed or refractory ALL and aHUS are far more comparable.
- 2.4 The cost for the first nine days of the first cycle of blinatumomab would be \$ [REDACTED] (assuming dosage requires four vials; the cost would be \$ [REDACTED] if one vial per day was used) and \$ [REDACTED] for two days of the second cycle (two vials). This would be offset for the hospitals by patients having a shorter length of stay compared to standard of care treatments.
- 2.5 The submission proposed a three-part listing: initiation, first continuation and second continuation. The treatment aim of blinatumomab is to achieve a complete remission, which improves eligibility for patients to receive allogeneic haematopoietic stem cell transplant (HSCT). The second continuation listing is for patients who achieve a response and are ineligible or awaiting HSCT. The submission considered that the majority of the patients would not receive the full five treatment cycles.
- 2.6 It was unclear whether blinatumomab would be recommended for retreatment following relapse. The pivotal study, MT103-211, allowed retreatment with blinatumomab after haematological relapse during the follow-up period, however, the National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2014), state that for a relapsed or refractory patient, use of a different regimen not previously used is advised, which would imply no further treatment with blinatumomab. Retreatment was not considered in the economic model or financial estimates. The PSCR (p2) noted that the proposed listing does not prohibit retreatment with blinatumomab but the sponsor would welcome advice from the PBAC in this regard.
- 2.7 The submission presented a cost-utility analysis compared to standard of care chemotherapy (represented in the economic model and financial estimates by FLAG (fludarabine, cytarabine, granulocyte-colony stimulating factor) + idarubicin).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **3 Background**

- 3.1 Blinatumomab was granted orphan designation by the TGA for the treatment of B-precursor Acute Lymphoblastic Leukaemia (ALL) in November 2013.
- 3.2 This submission was made under TGA/PBAC Parallel Process. At the time of evaluation, the clinical evaluation report was available. Blinatumomab was scheduled for consideration by the TGA at the December 2015 Advisory Committee on Prescription Medicines (ACPM) meeting for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia, however blinatumomab received a positive TGA Delegate's Overview in October 2015 and at that time, the Delegate advised that it did not require the advice

of the ACPM. As such, blinatumomab will be listed on the ARTG subject to agreement on the finalised Product Information.

- 3.3 Blinatumomab had not been considered by PBAC previously.

#### **4 Clinical place for the proposed therapy**

- 4.1 Ph- B-precursor ALL affects the lymphoblasts that are derived from lymphoid stem cells. The primary aim of ALL treatment is to induce and maintain remission and allow for an allogeneic HSCT. HSCT is considered the only potential cure for ALL. At present the only treatment options are investigational combination chemotherapy regimens followed by allogeneic HSCT, if patients achieve a response. Oriol (2010) reported an overall survival at one year of 24% and at five years of 10%, with a median age at relapse of 33 years. Blinatumomab is recommended for relapsed or refractory disease. The submission stated that blinatumomab would increase the probability of achieving a complete response, increasing the proportion of patients eligible for allogeneic HSCT.
- 4.2 The submission proposed that blinatumomab be used in the treatment of relapsed or refractory Ph- B-precursor ALL patients. It was not indicated for first-line treatment.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

#### **5 Comparator**

- 5.1 Standard of care chemotherapies for relapsed or refractory Ph- B-precursor ALL, including:
- FLAG ± anthracycline (e.g. idarubicin or amsacrine);
  - High-dose methotrexate in combination with pegylated-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents; and
  - High-dose cytarabine (HiDAC) base chemotherapy.
- 5.2 The ESC considered this was the appropriate comparator.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

#### **6 Consideration of the evidence**

##### **Sponsor hearing**

- 6.1 The sponsor requested a hearing for this item. The clinician described the high unmet clinical need for a safer alternative to chemotherapy for this patient group to achieve complete remission, as well as potentially being a less toxic bridge to stem-cell transplant. The clinician addressed concerns around neurotoxicity with blinatumomab, considering that it may be reversible and unlikely to reoccur on re-initiation. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

## Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

## Clinical studies

6.3 The submission was based on two single arm, Phase II studies assessing the efficacy of blinatumomab. To enable comparison, the submission also included a retrospective historical control study. The studies were:

- MT103-211: pivotal study, N = 225;
- MT103-206: dose-finding study, N = 36; and
- 20120310: retrospective historical control study, N = 1,139.

6.4 Details of the studies presented in the submission are provided in the table below.

**Table 1: Studies presented in the submission**

Study ID	Protocol title/ Publication title	Publication citation
<b>Non-randomised studies</b>		
MT103-211	Primary analysis: An open-label, multicentre, Phase II study to evaluate efficacy and safety of the bi-specific T cell engager (BiTE®) antibody blinatumomab in adult patients with relapsed/refractory B-precursor ALL.	11 July 2014
	Secondary analysis: An open-label, multicentre, Phase II study to evaluate efficacy and safety of the bi-specific T cell engager (BiTE®) antibody blinatumomab in adult patients with relapsed/refractory B-precursor ALL.	19 February 2015
	Topp MS, Gokbuget N, Stein AS, <i>et al.</i> Safety and activity of blinatumomab for adult patient with relapsed or refractory B-precursor acute lymphoblastic leukaemia: A multicentre, single-arm, Phase II study.	2014 <i>Lancet Oncol.</i> 16(1);57-66.
MT103-206	An open-label, multicentre, exploratory Phase II study to evaluate the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab in adult patients with relapsed/refractory B-precursor ALL.	2013
	Topp MS, Gokbuget N, Zugmaier G, <i>et al.</i> Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia.	2014 <i>J Clin Oncol.</i> 32(36):4134-4142
<b>Retrospective historical study</b>		
20120310	An analysis of historical data on haematological remission rates and survival among adult patients with relapsed or refractory B-precursor ALL.	2014

Source: Table B.2-2, p52 of the submission

ALL = acute lymphoblastic leukaemia

6.5 Currently, a randomised controlled trial is being conducted (TOWER) comparing blinatumomab with standard of care chemotherapy. This trial was excluded by the submission as no results were available. The expected primary completion date of this trial is August 2016. The PSCR (p6) advised the results will not be available until June 2017. The Pre-PBAC response (p2) provided information on what data from the TOWER trial will be reported to help further inform PBAC. The primary endpoint of the TOWER study is overall survival and key secondary endpoints include complete response within 12 weeks, event free survival, duration of complete response, minimal residual disease remission within 12 weeks, quality of life, HSCT with or

without blinatumomab treatment, incidence of adverse events and 100-day mortality after HSCT.

6.6 The key features of the non-randomised studies are summarised in the table below.

**Table 2: Key features of the included evidence**

Study	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MT103-211	FAS = 225 PAS = 189	Single-arm, OL, MC 33 weeks (Follow-up to 3 years)	High	<ul style="list-style-type: none"> <li>• Adult;</li> <li>• &gt; 10% blasts in bone marrow;</li> <li>• Refractory disease;</li> <li>• Relapsed disease with 1<sup>st</sup> remission duration of ≤ 12 months; relapse after 1<sup>st</sup> salvage therapy; or relapse ≤ 12 months after allogeneic HSCT</li> </ul>	CR, CRh*; HSCT rate; OS	Yes
MT103-206	36	Single-arm, OL, MC 33 weeks (Follow-up to 3 years)	High	<ul style="list-style-type: none"> <li>• Adult;</li> <li>• &gt; 5% blasts in bone marrow;</li> <li>• Refractory disease;</li> <li>• Relapsed disease with CR of &gt; 28 days</li> </ul>	CR, CRh*; HSCT rate; OS	No
20120310	1,139	Retrospective historical control, pooled analysis, MC (Follow-up to 5 years)	High	<ul style="list-style-type: none"> <li>• Adult;</li> <li>• In first relapse or salvage treatment after first remission of ≥ 12 months;</li> <li>• Refractory to initial treatment;</li> <li>• Relapse ≤ 12 months after HSCT</li> </ul>	CRsg	Yes

Source: compiled during the evaluation

CR = complete remission; CRh\* = complete remission with partial haematological recovery; CRsg = complete remission as per study definition; FAS = full analysis set; HSCT = haematopoietic stem cell transplant; MC = multi-centre; OL = open-label; OS = overall survival; PAS = primary analysis set

6.7 The MT103-211 and MT103-206 studies were prospective, open-label, single arm studies. Study 20120310 was a retrospective study which sought to identify response rate and overall survival in a comparable patient population to MT103-211. Analyses of this study were performed using a weighted distribution of key patient prognostic factors to match MT103-211, (i.e. age (<35 years, ≥35 years); prior lines of treatment; and prior allogeneic HSCT). The submission and study protocol for 20120310 do not justify why these variables were chosen.

6.8 The ESC considered there is likely significant bias due to residual confounding, despite the adjustment to the patient prognostic factors listed above. Bone marrow blast at baseline was a significant pre-specified prognostic factor for response and the OS in MT103-211, with a lower response rate in patients with >50% blasts. In the historical controls, there are a lower percentage of patients with <50% blasts and it is therefore unclear whether the response rate would have been different. This may underestimate the efficacy of standard of care.

6.9 Platelet levels were another significant prognostic factor of response and OS highlighted by MT103-211. This was also not included in the 'key' variables adjusted

for. Insufficient detail is provided to assess whether or not adjusting for this variable has significantly biased the estimate of treatment effect. Sufficient sensitivity analyses were not undertaken regarding the effect of adjusting for these other variables on the treatment effect estimate (and subsequently on the estimated ICER).

### Comparative effectiveness

- 6.10 The key outcomes from the non-randomised studies used in the submission are presented in the table below. Approximately ██████ of patients in the historical control study were diagnosed between the year 1990 and 1999 when treatment practices were different. The blinatumomab studies were conducted in 2010 and 2011. This may have resulted in an underestimation of the effects of standard of care chemotherapy. The PSCR (p2) argued that given the rarity of ALL it was important to include as much historical control data as was considered comparable. To justify the inclusion of the 'earlier' historical data (1990-1999), the PSCR presented an analysis of outcomes by calendar period from the historical comparator data, which showed that there was ██████ in terms of complete remission (CR), and ██████ ██████ in overall survival, when data from the earlier (1990-1999) and later (2000+) time periods are compared. The ESC noted the analysis, but remained concerned that the historical data may underestimate response in the comparator arm (and therefore overestimate the relative benefit of blinatumomab treatment).
- 6.11 The ESC noted the PSCR (p1) suggestion that the historical cohort data are considered comparable as no significantly new treatments or improvements for relapsed or refractory ALL had emerged since the 1990's. However, ESC still considered the data post-2000 to be informative (an additional column was added to the results table below). It was noted there have been major changes in salvage therapies, supportive care treatments and allogeneic HSCT procedures over the past 25 years, including the introduction of broad spectrum antibiotics (e.g. piperacillin-tazobactam, carbapenems, and third-, fourth-, and fifth-generation cephalosporins), antifungals (e.g. caspofungin, voriconazole, micafungin), advanced blood transfusion techniques and better transplant facilities.

Table 3: Key results across the non-randomised studies

	MT103-211 <sup>a</sup>		MT103-206	20120310	
				Weighted <sup>b</sup>	post-2000 (unweighted)
N	PAS: 189	FAS: 225	36	-	-
Median observation time	17.7 months	17.0 months	12.1 months	-	-
CR + CRh* (or CRsg), n (%) (95% CI)	83 (43.9%) (0.37, 0.51)	99 (44.0%) (0.37, 0.51)	25 (69.4%) (0.52, 0.84)	24.0% (0.20, 0.27) <sup>c</sup>	█████% (█████) <sup>c</sup>
Total HSCT rate, n (%) (95% CI)	52 (27.5%)	60 (26.7%)	18 (50.0%)	18% (0.15, 0.21) <sup>d</sup>	█████% (█████) <sup>d</sup>
HSCT following CR/CRh*/CRsg, n (%) (95% CI)	34 (17.9%)	39 (17.3%)	13 (52.0%)	7% (0.05, 0.09) <sup>d</sup>	NR
OS, months (95% CI)	6.4 (4.3, 7.7)	6.5 (4.7, 7.7)	9.8 (8.5, 14.9)	3.3 (2.8, 3.6) <sup>e</sup>	█████ (█████) <sup>e</sup>

Source: Table B.6-2, p96; Table B.6-4, p99; Table B.6-5, p100; Table B.6-7, p102; Table B.6-8, p107 of the submission; and Table 10-1, p109; Table 14-04-25-1, p521; Table 14-04-25-3, p524; Table 14-04-28-3, p538 of study MT103-211 Secondary Analysis CSR

CI = confidence interval; CR = complete remission; CRh\* = complete remission with partial haematological recovery; CRsg = complete remission as per study definition; FAS = full analysis set; HSCT = haematopoietic stem cell transplant;

OS = overall survival; PAS = primary analysis set

<sup>a</sup> Results from the secondary analysis, which included data collected until 20 June 2014

<sup>b</sup> Results weighted to study MT103-211 population

<sup>c</sup> N = 694 for weighted, N= [redacted] for 2000+

<sup>d</sup> N = 808 for weighted, N= [redacted] for 2000+

<sup>e</sup> N = 1,112 for weighted, N= [redacted] for 2000+

- 6.12 For the treatment of relapsed or refractory Ph- B-precursor ALL, it appeared that blinatumomab was more effective than standard of care chemotherapy in terms of complete remission (CR) rates, complete remission with partial haematological recovery (CRh\*) rates, allogeneic HSCT rates and overall survival. The overall survival in Study 20120310 was somewhat sensitive to subgroup analyses presented in the study report (e.g. USA vs. Europe, 1990-1999 vs. 2000-2012, prior lines of treatment, and age at treatment), with point estimates between [redacted] and [redacted] months. For patients with an initial diagnosis between 1990 and 1999, the median overall survival was [redacted] months (95% confidence interval (CI): [redacted] to [redacted] months), while for those patients diagnosed after 2000 it was [redacted] months (95% CI: [redacted] to [redacted] months). Therefore, current standard of care in Australian practice might result in higher effectiveness than that presented in the retrospective historical control study.
- 6.13 The PSCR (p2, Table 1) provided results of weighted OS in >2000 period of [redacted] ([redacted], [redacted]) months compared to [redacted] ([redacted], [redacted]) with inclusion of data of <2000. The weighted data >2000 could not be verified.
- 6.14 There was no direct comparative evidence for efficacy, and given the lack of exchangeability between the study data, the submission did not provide any statistical analyses of the naïve indirect comparisons. Additionally, patients in study MT103-211 had more severe disease than those in the proposed PBS population, therefore the results from this study might be an underestimation of the true effect in the proposed PBS population.

### Comparative harms

- 6.15 There were no safety endpoints in the historical study, 20120310; therefore, the submission did not undertake a comparative safety analysis. Table 4 presents a summary of the treatment emergent adverse events from the blinatumomab studies (MT103-211 and MT103-206).

**Table 4: Treatment emergent adverse events from the blinatumomab studies**

N	MT103-211, n (%)		MT103-206, n (%)
	PAS = 189	FAS = 225	36
Treatment emergent adverse events			
All	188 (99.5%)	224 (99.6%)	36 (100%)
Grade ≥ 3	155 (82.0%)	185 (82.2%)	27 (75%)
Grade ≥ 4	84 (44.4%)	101 (44.9%)	17 (47%)
Serious	121 (64.0%)	145 (64.4%)	25 (69%)
Fatal	28 (14.8%)	34 (15.1%)	6 (17%)
Treatment emergent adverse events related to blinatumomab			
All	166 (87.8%)	197 (87.6%)	36 (100%)
Grade ≥ 3	105 (55.6%)	124 (55.1%)	23 (64%)
Grade ≥ 4	42 (22.2%)	53 (23.6%)	12 (33%)
Serious	69 (36.5%)	81 (36.0%)	17 (47%)
Fatal	3 (1.6%)	4 (1.8%)	1 (3%)

*Public Summary Document – November 2015 PBAC Meeting*

Source: Table B.6-14, p120 of the submission  
FAS = full analysis set; PAS = primary analysis set

- 6.16 The most common serious adverse events reported in study MT103-211 and assessed to be related to blinatumomab were pneumonia (8.5%) and febrile neutropenia (3.2%). In study MT103-206 the most common serious adverse events attributed to blinatumomab therapy were cytokine release syndrome, encephalopathy and tremor, each experienced by 8.3% of patients.
- 6.17 Common treatment emergent adverse events considered to be related to blinatumomab treatment were pyrexia, fatigue, nausea, headache and tremor.
- 6.18 For the comparison with standard of care chemotherapy, the submission presented the rates of serious adverse events as reported in the two blinatumomab studies and in the Australian product information sheets for the medications included in the FLAG ± anthracycline, HiDAC and high-dose methotrexate regimens. The submission reported that the incidence of severe adverse events for all standard of care chemotherapies were 100%, compared to 36% for blinatumomab. It should be noted that the rate for blinatumomab was for treatment-related emergent adverse events, rather than all serious adverse events.

***Benefits/harms***

- 6.19 A summary of the comparative benefits of blinatumomab versus standard of care chemotherapy is presented in the table below. There were no comparative harms presented in the submission.

**Table 5: Summary of comparative benefits and harms for blinatumomab and standard of care chemotherapy**

<b>BENEFITS</b>						
Study	Blinatumomab	SOC	RR (95% CI)	Event rate/100 patients <sup>a</sup>		RD (95% CI)
				Blinatumomab	SOC	
<b>CR + CRh* (or CRsg), n</b>						
MT103-211 (FAS)	99/225	-	-	44	-	-
MT103-206	25/36	-	-	69	-	-
20120310	-	NR <sup>b</sup>	-	-	24	-
<b>Total allogeneic HSCT rate, n</b>						
MT103-211 (FAS)	60/225	-	-	27	-	-
MT103-206	18/36	-	-	50	-	-
20120310	-	NR <sup>b</sup>	-	-	18	-
<b>Overall Survival, median (months)</b>						
	<b>Blinatumomab</b>	<b>SOC</b>	<b>Absolute Difference</b>		<b>HR (95% CI)</b>	
MT103-211 (FAS)	6.5 (4.7, 7.7)	-	-		-	
MT103-206	9.8 (8.5, 14.9)	-	-		-	
20120310	-	3.3 (2.8, 3.6)	-		-	
<b>HARMS</b>						
Study	Blinatumomab	SOC	RR (95% CI)	Event rate/100 patients <sup>a</sup>		RD (95% CI)
				Blinatumomab	SOC	
<b>Grade ≥ 3 treatment-related emergent adverse events, n</b>						
MT103-211 (FAS)	124/225	-	-	55	-	-
MT103-206	23/36	-	-	64	-	-
20120310	-	NR	-	-	-	-
<b>Grade ≥ 4 treatment-related emergent adverse events, n</b>						
MT103-211 (FAS)	53/225	-	-	24	-	-
MT103-206	12/36	-	-	33	-	-
20120310	-	NR	-	-	-	-
<b>Fatal treated-related events, n</b>						
MT103-211 (FAS)	4/225	-	-	2	-	-
MT103-206	1/36	-	-	1	-	-
20120310	-	NR	-	-	-	-

Source: compiled during the evaluation

CI = confidence interval; CR = complete remission; CRh\* = complete remission with partial haematological recovery; CRsg = complete remission per study group definition; FAS = full analysis set; HR = hazard ratio; HSCT = haematopoietic stem cell transplant; NR = not reported; RD = risk difference; RR = relative risk; SOC = standard of care

<sup>a</sup> Median duration of follow-up: MT103-211 = 6.5 months; MT103-206 = 8.5 months

<sup>b</sup> Results weighted to study MT103-211 population; only patients with available endpoint data were included

6.20 Based on a naïve indirect comparison with no common comparator, the comparison of blinatumomab with standard of care chemotherapy:

- appeared to result in improved CR, CRh\*, allogeneic HSCT rates and overall survival; however, the difference was uncertain as the comparative effectiveness could not be quantified; and
- was not robustly informative with respect adverse events; although, the risk of uncommon neurologic events and cytokine release syndrome at the initiation of blinatumomab treatment requires hospitalisation for the first nine days of Cycle 1 and the first two days of Cycle 2.

**Clinical claim**

- 6.21 The submission described blinatumomab as superior in terms of comparative effectiveness and superior in terms of comparative safety over standard of care combination chemotherapies.
- 6.22 The ESC considered the claim for superior efficacy was poorly supported.
- The efficacy of blinatumomab appeared to be better compared to standard of care salvage chemotherapy regimens; however, the submission provided a naïve, indirect comparison using a historical retrospective study as the control, and could not quantify the comparative effectiveness.
  - Although the population from the pivotal study, MT103-211, potentially had more severe disease compared to the proposed PBS population, and the efficacy results from this study might have been an underestimation of the true effect of blinatumomab, bias might have favoured blinatumomab.
  - In addition, as patients in the historical study were included if they were diagnosed in 1990 or later, the results of the comparative study may have been an underestimation of the true effect of current standard of care chemotherapy regimens.
- 6.23 The ESC considered the claim of superior comparative safety is difficult to assess given the difference in the type and timing of adverse events between blinatumomab and standard of care.
- The submission did not present any safety outcomes for the comparator arm as no safety endpoints were available from the historical retrospective study.
  - Blinatumomab requires hospitalisation for the first nine days of Cycle 1 and the first two days of Cycle 2 due to the risk of neurologic adverse events and of cytokine release syndrome.
- 6.24 The PBAC considered that the claim of superior comparative effectiveness and superior comparative safety was unable to be determined from the data presented.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Economic analysis**

- 6.25 The ESC considered the model was not reliable and likely optimistic given the estimated extent of benefit relies on non-comparative historical clinical data.
- 6.26 The submission presented a decision analytic model that used area under the curve methods to estimate overall survival. The stepped economic evaluation was a cost-utility analysis. Blinatumomab treatment was compared with standard of care chemotherapy in patients with relapsed or refractory Ph- B-precursor ALL. A summary of the model structure is presented below.

**Table 6: Summary of model structure and rationale**

Time horizon	20 years in the model versus 25 months in study MT103-211 and 60 months in study 20120310. The PSCR (p3) suggested the 20 year time horizon is appropriate as the median age of patients is 35 and a proportion is expected to achieve normal life expectancy.
Outcomes	Life years gained and QALYs
Methods used to generate results	Decision analytic model that used area under the curve methods (trapezoidal method) to estimate overall survival.
Cycle length	Monthly for the first 5 years and then yearly until 20 years, with half-cycle correction.
Discount rate	5% for benefits and costs
Software package	Excel 2010 (v14)

Source: compiled during the evaluation

QALY = quality-adjusted life year

6.27 A number of the model inputs could not be verified (e.g. non-responder mean survival, time to death for initial responders who relapse, percentage of patients without a response, the proportion of patients who had a second cycle of standard of care chemotherapy, cost of HSCT follow-up). The structure of the economic model omitted the following key factors:

- it did not consider patients who received further salvage therapies after not responding to or relapsing after treatment. The PSCR states (p.2) that subsequent therapies will occur similarly in both arms and as stated in the commentary there are some overestimates as well as underestimates which would neutralise cost differences. The ESC considered that the cost differences should still be included in the model along with utility consequences.
- it did not consider allogeneic haematopoietic stem cell transplant (HSCT) as a separate health state – it could be expected that patients undergoing HSCT would have a lower utility than the 'before relapse' utility of [REDACTED]. The PSCR (p.3) used utility values from a [REDACTED] to assess the impact of any utility decrement associated with HSCT.
- the assumption that patients who responded would do so immediately (and have utility of [REDACTED]).
- disutilities and costs for AEs are selectively included.

6.28 Table 7 presents the key drivers of the economic model.

**Table 7: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	20 years; assumed from 2 year and 5 year study durations	High; favours blinatumomab
Utility values	TTO study did not provide health state vignettes; therefore it was not possible to confirm whether the health states were appropriately described. The vignettes provided in the PSCR (p.5, Table 2) may not adequately capture the experience. For instance, it may have been more appropriate to have everyone start as relapsed or refractory with the opportunity to improve from that health state rather than collapsing into 'before relapse' (C & D) and 'after relapse' (A, E & B). Also, the model did not consider the utility of patients undergoing allogeneic HSCT.	Unclear; likely to favour blinatumomab
Inpatient costs	Blinatumomab = \$ [REDACTED] (did not include prophylactic and treatment costs associated with neurologic events and cytokine release syndrome, therefore likely to be an underestimate); SOC = \$ [REDACTED]	High; favours blinatumomab

Source: compiled during the evaluation

HSCT = haematopoietic stem cell transplant; SOC = standard of care; TTO = time trade-off

- 6.29 Based on the number of patients commencing each cycle of blinatumomab in study MT103-211, the submission estimated that 52% of patients would receive Cycle 2 of blinatumomab and 41% of patients would receive additional cycles (41% = 22.8% of patients commence Cycle 3 + 11.6% commence Cycle 4 + 6.9% commence Cycle 5).
- 6.30 The ESC considered the cost of blinatumomab administration was underestimated as the submission did not consider that patients would be hospitalised due to risk of very serious adverse events. The comments in the PSCR (p3) describing the difference between hospital costs for very high risk patients only increasing the ICER by [REDACTED]% were considered unhelpful in the context of an unreliable base case. This may also still underestimate the true cost, as expensive medications might be required for these adverse events. For instance, treatment of cytokine release syndrome often requires more than blinatumomab discontinuation or corticosteroids. It has been reported in the literature (Maude 2014)<sup>1</sup> that the interleukin-6 inhibitor tocilizumab might be successful in treatment of this condition. Tocilizumab is not TGA registered or PBS listed for this indication.
- 6.31 The results of the stepped economic evaluation are presented in the table below.

<sup>1</sup> Maude SL, Barret D, Teachey DT et al. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014;20(2):119-122

**Table 8: Results of the stepped economic evaluation**

Step and component	Blinatumomab	Standard of care	Increment
<b>Step 1: Study-based costs and outcomes (2 year time horizon)</b>			
Costs	\$█	\$█	\$█
Life years gained	0.794	0.50	0.29
<b>Incremental cost/extra life year gained</b>			\$█
<b>Step 2: Modelled evaluation (time horizon increased to 20 years)</b>			
Costs	\$█	\$█	\$█
Life years gained	3.085	1.49	1.60
<b>Incremental cost/extra life year gained</b>			\$█
<b>Step 3: Modelled evaluation (discount rate of 5% applied)</b>			
Costs	\$█	\$█	\$█
Life years gained	2.219	1.11	1.11
<b>Incremental cost/extra life year gained</b>			\$█
<b>Step 4: Modelled evaluation (additional costs included: HSCT, CR follow-up, palliative care)</b>			
Costs	\$█	\$123,456	\$█
Life years gained	2.219	1.11	1.11
<b>Incremental cost/extra life year gained</b>			\$█
<b>Step 5: Modelled evaluation (average utility of 0.728 applied to 'before relapse' and 'after relapse' states)</b>			
Costs	\$█	\$█	\$█
QALYs	1.615	0.811	0.80
<b>Incremental cost/extra QALY gained</b>			\$█
<b>Step 6: Modelled evaluation (utility of 0.84 for 'before relapse' and 0.35 for 'after relapse' applied)</b>			
Costs	\$█	\$█	\$█
QALYs	1.679	0.75	0.93
<b>Incremental cost/extra QALY gained</b>			\$█

Source: Table D.5-2, p238 of the submission; and Blin\_v\_1\_0.j.xlsm Excel workbook

CR = complete remission; HSCT = haematopoietic stem cell transplant; QALY = quality-adjusted life year

- 6.32 The submission estimated an incremental cost-effectiveness ratio (ICER) of \$75,000 - \$105,000 per life year gained and of \$75,000/QALY - \$105,000/QALY. The ESC agreed with the commentary that the results of the economic model were unreliable due to a number of assumptions and omissions made in the model.
- 6.33 The table below provides the results of the key univariate sensitivity analyses presented by the submission and conducted during the evaluation. ESC considered these one-way sensitivity analyses to have limited value given they rely on an uncertain and optimistic base case.

**Table 9: Key sensitivity analyses**

Univariate analyses	Incremental cost	Incremental effectiveness	ICER
<b>Base case</b>	\$█	0.934	\$█
<b>Structural issues</b>			
Time horizon (base case = 20 years)			
5 years	\$█	0.43	\$█
10 years	\$█	0.64	\$█
40 years	\$█	1.20	\$█
<b>Parameter changes</b>			
Blinatumomab inpatient cost (base case = \$█)			
\$█ (i.e. x 0.5)	\$█	0.93	\$█
\$█ (i.e. x 1.5)	\$█	0.93	\$█
Blinatumomab AR-DRG code R60A in cycle 1 (base case = no) <sup>a</sup>			
Yes	\$█	0.93	\$█

Univariate analyses	Incremental cost	Incremental effectiveness	ICER
SOC inpatient cost (base case = \$ [redacted])			
\$ [redacted] (i.e. x 0.5)	\$ [redacted]	0.93	\$ [redacted]
\$ [redacted] (i.e. x 1.5)	\$ [redacted]	0.93	\$ [redacted]
Blinatumomab drug cost (base case = \$ [redacted]/1,156 µg/46 vials)			
\$ [redacted] (i.e. x 0.9)	\$ [redacted]	0.93	\$ [redacted]
\$ [redacted] (i.e. x 1.1)	\$ [redacted]	0.93	\$ [redacted]
\$ [redacted] (assuming no wastage/[redacted] vials)	\$ [redacted]	0.93	\$ [redacted]
\$ [redacted] (assuming average use of [redacted] µg/[redacted] vials)	\$ [redacted]	0.93	\$ [redacted]
% of blinatumomab non-responders (base case = 0.572)			
0.458 (i.e. x 0.8)	\$ [redacted]	0.93	\$ [redacted]
0.686 (i.e. x 1.2)	\$ [redacted]	0.94	\$ [redacted]
0.56 (FAS population in MT103-211)	\$ [redacted]	0.93	\$ [redacted]

Source: Blin\_v\_03j.xlsm, Excel Economic Model file

AR-DRG = Australian refined diagnosis-related group; FAS = full analysis set; ICER = incremental cost-effectiveness ratio; SOC = standard of care; FAS = full analysis set

<sup>a</sup> This was to reflect the serious safety risk for patients treated with blinatumomab in the first cycle, i.e. uncommon neurologic events and cytokine release syndrome; R60A = acute leukaemia with catastrophic complication or co-morbidity

- 6.34 The results of the sensitivity analyses showed that the economic model was most sensitive to the time horizon, inpatient costs associated with standard of care chemotherapy, inpatient costs associated with blinatumomab (specifically whether Australian refined diagnosis-related group (AR-DRG) R60A was included), and number of blinatumomab vials required.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

**Drug cost/patient/treatment: \$ [redacted]**

- 6.35 The estimated cost per blinatumomab treatment would be \$ [redacted], assuming an average total dose of [redacted] µg supplied in [redacted] vials. This was based on the dose in the key clinical study MT103-211, where all patients commenced Cycle 1, 51% commenced the second cycle and 41% of patients would receive additional cycles (41% = 22.8% of patients commence Cycle 3 + 11.6% commence Cycle 4 + 6.9% commence Cycle 5). This cost should be once per lifetime as retreatment is not recommended in the NCCN guidelines.

- 6.36 The ESC considered it would be informative to know how many patients in the trial remained on treatment after the first cycle and what were the reasons for discontinuing therapy (ie no response, response-then HSCT, relapse, death). This was provided in the Pre-PBAC response (p3).

**Estimated PBS usage & financial implications**

- 6.37 This submission was not considered by DUSC. The submission used an epidemiological approach (incidence population) to estimate the extent of use of blinatumomab and the financial implications to the PBS/RPBS and MBS.

**Table 10: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated					
Vials <sup>a</sup>					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
<b>Estimated total net cost</b>					
<b>Net cost to PBS/RPBS/MBS</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>

Source: Table E.2-4, p262; Table E.4-1, p263 of the submission

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

<sup>a</sup> Assuming 46 vials per treatment course as estimated by the submission

*The redacted table above shows that the number of patients treated with blinatumomab is estimated to be less than 10,000 per year at a net cost to the PBS of less than \$10 million per year.*

6.38 The cost to the PBS/RPBS could be higher or lower than presented in the submission because:

- For the estimate of patients with relapsed or refractory Ph- B-precursor ALL:
  - the number of patients cured after first line treatment may be higher or lower;
  - there may be a small number of patients who had relapsed after more than one line of treatment that were not included in the calculations.
- The number of patients treated with blinatumomab might be higher (the submission assumed an % market uptake).
- The number of vials of blinatumomab dispensed may have been under or overestimated as:
  - efficient use of vials in the first cycle was not considered;
  - the submission assumed that all vials would be dispensed through the PBS. This may not be valid as patients would be in hospital for 11 days, and PBAC might decide that these vials would not be reimbursed by the PBS;
  - the proportion eligible for HSCT and the time before a patient would receive HSCT in clinical practice might be different from the values in the key clinical study MT103-211, resulting in patients receiving more or less cycles of blinatumomab.
- Increased allogeneic HSCT rates following CR or CRh\* with blinatumomab therapy would be expected to result in an increase in PBS costs for post HSCT medications.

### **Financial Management – Risk Sharing Arrangements**

6.39 The submission argued that the patient population was likely to be small (approximately patients per year) and noted that the PBAC may consider whether the rule of rescue would apply. Blinatumomab may not meet criterion one for rule of rescue, because alternative therapies are available.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of blinatumomab for the treatment of relapsed or refractory Ph- B-precursor acute lymphoblastic leukaemia (ALL) due to uncertainties in comparative clinical effectiveness and a high and uncertain ICER.
- 7.2 The PBAC noted the high clinical need for an effective alternative to chemotherapy in this patient population, noting that blinatumomab may not be a cure for many patients, but rather provide a “bridge” to enable some patients to undergo a potentially curative allogeneic haematopoietic stem cell transplant (HSCT). The PBAC considered that the high clinical need for blinatumomab meant a resubmission should not wait until the results of the phase 3 randomised study, TOWER, are available in mid-2017.
- 7.3 The PBAC agreed with ESC that blinatumomab is more analogous to infliximab for the treatment of patients with acute ulcerative colitis, which is not subsidised in the inpatient setting, than to eculizumab for atypical haemolytic uraemic syndrome (aHUS) which is subsidised in the inpatient setting. Given the PBAC considered that PBS subsidised blinatumomab should not be provided to inpatients, the maximum quantities and repeats should be adjusted to account for the first two cycles of treatment being provided in hospital, i.e. maximum quantity of 1 vial and 22 repeats for cycle 1; 27 repeats for cycle 2; and 28 repeats for cycles 3-5. This avoids delays in commencing treatment while waiting for approval of a written authority while minimising the risks of longer term cost exposure to public hospitals or health funds, as ambulatory treatment can be PBS-subsidised. This arrangement also avoids a precedent for PBS funding of inpatient chemotherapy in public hospitals.
- 7.4 The PBAC noted the proposed restriction and considered that an initial written authority would be appropriate, with a telephone authority suitable for first and second continuation. The PBAC considered that the restriction should explicitly exclude patients with CNS disease, as per the clinical studies. The PBAC further considered that retreatment following relapse should not be permitted based on current evidence and guidelines.
- 7.5 The PBAC agreed with the ESC that standard of care chemotherapies were the appropriate comparator.
- 7.6 In assessing the clinical evidence, the PBAC considered that the most informative analysis for estimating comparative effectiveness would be against the weighted post-2000 control data, noting that the analysis completed in the Pre-PBAC response (Table 1, p1) had not been evaluated. The PBAC agreed with the ESC that bone marrow blast count and platelet levels should be matched in the weighted comparison.
- 7.7 The PBAC considered that the clinical claim of superior efficacy was difficult to assess, noting that blinatumomab has clear efficacy in a minority of patients and appears superior to current salvage therapy, however the magnitude of improvement in long-term outcomes cannot be determined readily from the data presented.
- 7.8 The PBAC noted that no comparative safety outcomes were provided. The PBAC considered that blinatumomab and standard of care chemotherapy have different yet

significant adverse event profiles, and as such the comparative adverse event data from TOWER will be informative for a robust assessment of comparative harms.

- 7.9 The PBAC considered that the claim of superior safety was difficult to assess and that toxicity would vary depending on the clinical state of a patient when treatment is commenced. The PBAC noted blinatumomab is associated with the important major toxicity of cytokine release syndrome and this requires access to non-conventional therapy and inpatient support.
- 7.10 The PBAC agreed with concerns raised by the evaluation and the ESC regarding the economic model, considering that it was likely to be optimistic and was not reliable for decision making. The PBAC considered that refinement of the weighted analysis and better definition of costs of toxicity of treatment would generate a more reliable estimate of the incremental costs and benefits of blinatumomab. Without the comparative results of the TOWER study, which would be the preferred input into the economic model, residual uncertainty in a revised model could be dealt with by adjusting the price to mitigate risk to the Commonwealth.
- 7.11 The PBAC agreed with the ESC that the economic model should consider cost differences and utility consequences in patients who received further salvage therapies after not responding to or relapsing after treatment. The PBAC also noted the assumption in the economic model that patients who respond would do so immediately, but considered that this should be further justified.
- 7.12 The PBAC considered that the cost of blinatumomab administration was likely to be underestimated, particularly surrounding costs of managing adverse events.
- 7.13 The PBAC considered that the 20 year time horizon in the economic model was appropriate, however considered that more detailed input data on the costs of allogeneic HSCT, and evidence based estimates of life expectancy post allogeneic HSCT would be required to improve reliability of the model.
- 7.14 The PBAC considered that an ICER of \$75,000/QALY - \$105,000/QALY gained was unacceptably high, particularly as this is highly uncertain and likely to underestimate the true ICER. The PBAC determined the request to consider the rule of rescue was premature without more definitive evidence of rescue. Even then, rule of rescue would be difficult to justify unless a major difference in the rate of allogeneic HSCT is demonstrated.
- 7.15 The PBAC considered that estimates of use and financial implications are highly uncertain but noted that total numbers are likely to be small.
- 7.16 The PBAC is supportive of expediting the listing of blinatumomab with a managed access program, or similar arrangement, if the weighted post-2000 control data can be used to inform a revised economic evaluation. The PBAC considered that, due to the various issues with the model, any resubmission should be a major submission to allow for evaluation.
- 7.17 The PBAC noted that the submission is eligible for an Independent Review.

Outcome:

Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

Amgen is pleased with the PBACs acknowledgement of the high clinical need and that blinatumomab will provide a “bridge” to enable some patients to undergo a potentially curative allogeneic haematopoietic stem cell transplant.

While Amgen is disappointed with the PBAC's initial recommendation, we will continue to seek reimbursed access at the earliest possible opportunity for adults with acute lymphoblastic leukaemia. Amgen agrees with the PBAC that an innovative solution may be the most expeditious alternative to provide access as soon as possible to patients in significant need.