

**7.01 BLINATUMOMAB,
Injection 38.5 microgram [1 vial] and inert substance solution
[10 mL vial], 1 pack,
Blincyto[®], Amgen Australia Pty Ltd**

1 Purpose of Application

1.1 The resubmission requested a Section 100 (Highly Specialised Drug Program) listing of blinatumomab for the treatment of relapsed or refractory Philadelphia chromosome negative (Ph-) B-precursor acute lymphoblastic leukaemia (ALL). The first submission was considered in November 2015.

2 Requested listing

2.1 The resubmission proposed a three-part listing: initiation (one cycle), first continuation (one cycle) and second continuation (up to three cycles). The second continuation listing is for patients who would be ineligible or awaiting allogeneic haematopoietic stem cell transplant (HSCT). An abridged requested PBS listing is presented below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Initiation

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BLINATUMOMAB				Blincyto Amgen
Powder for injection 38.5 microgram	Up to 28	0	\$ [REDACTED] (published)	
with intravenous solution stabiliser	1	22	\$ [REDACTED] (effective)	

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing

Public Summary Document – July 2016 PBAC Meeting

Clinical criteria:	<p>Patient must have relapsed or refractory B-precursor ALL;</p> <p>AND</p> <p>Patient must be an adult;</p> <p>AND</p> <p>Patient must be The condition must be Philadelphia chromosome negative;</p> <p>AND</p> <p>Patient has must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2;</p> <p>AND</p> <p>Patient must have received an initial nine days of therapy in this treatment cycle as a hospital inpatient;</p> <p>AND</p> <p>Patient must have received intensive combination chemotherapy for the treatment of ALL for initial treatment or subsequent salvage therapy;</p> <p>AND</p> <p>Patient does must not have presence of active disease in the CNS or testis.</p>
---------------------------	--

First continuation

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BLINATUMOMAB				Blincyto Amgen
Powder for injection 38.5 microgram with intravenous solution stabiliser	Up to 28 1	0 26	\$ [REDACTED] (published) \$ [REDACTED] (effective)	

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	First continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required – Electronic

Public Summary Document – July 2016 PBAC Meeting

Clinical criteria:	<p>Patient must have received an initial prescription for blinatumomab for treatment of relapsed or refractory Philadelphia negative B cell Acute lymphoblastic leukaemia previously received PBS-subsidised initial treatment with this drug for this condition;</p> <p>AND</p> <p>Patient must not have progressive disease after the first cycle of blinatumomab therapy;</p> <p>AND</p> <p><i>Patient must have received two days of therapy in this treatment cycle as a hospital inpatient.</i></p>
---------------------------	---

Second continuation

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BLINATUMOMAB				Blinicyto Amgen
Powder for injection 38.5 microgram with intravenous solution stabiliser	Up to 28 1	0 27	\$ [REDACTED] (published) \$ [REDACTED] (effective)	

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	Second continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required – Electronic
Clinical criteria:	<p>Patient must have received an initial and continuing prescription for blinatumomab for treatment of relapsed or refractory Philadelphia negative B cell Acute lymphoblastic leukaemia previously received initial and continuing treatment with this drug for this condition;</p> <p>AND</p> <p>Patient must have demonstrated at least a CR complete remission or CRh* complete remission with partial haematological recovery after the first 2 cycles of blinatumomab therapy</p> <p>AND</p> <p>Patient is must be ineligible for stem cell transplant;</p> <p>OR</p> <p><i>Patient must be awaiting stem cell transplant.</i></p>
Prescriber Instructions	<i>No more than 3 cycles will be authorised.</i>

2.2 The proposed PBS restriction was the same as in the original submission, except for:

- the explicit exclusion of patients with central nervous system or testis disease; and
 - a [REDACTED]% reduction in the effective ex-manufacturer price to \$ [REDACTED] per vial.
- 2.3 Blinatumomab would be provided as an inpatient for the first nine days of Cycle 1 and the first two days of Cycle 2. The resubmission again requested PBS reimbursement for inpatient supply. In November 2015, the PBAC indicated that blinatumomab was more analogous to infliximab for the treatment of ulcerative colitis, which is not PBS reimbursed for inpatient use. The resubmission claimed that blinatumomab was more analogous to eculizumab for the treatment of atypical haemolytic uraemic syndrome, which is reimbursed in the inpatient setting.
- 2.4 To reflect the advice of the PBAC in November 2015 that PBS subsidised blinatumomab should not be provided to inpatients, a maximum quantity of 1 vial with 22 repeats for cycle 1, and 27 repeats for cycle 2, was proposed by the Secretariat.
- 2.5 The resubmission presented a cost-utility analysis comparing blinatumomab with standard care chemotherapy (represented in the economic model and financial estimates by fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG) plus idarubicin).

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

3 Background

- 3.1 TGA status: Blinatumomab was TGA registered on 9 November 2015 for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia.
- 3.2 Blinatumomab was considered by the PBAC once previously, in November 2015.
- 3.3 The table below presents a summary of the November 2015 submission, PBAC comments and the July 2016 resubmission.

Table 1: Summary of the original submission and current resubmission

	November 2015 submission	July 2016 resubmission
Requested PBS listing	<ul style="list-style-type: none"> Section 100, Highly Specialised Drug listing for the treatment of relapsed or refractory Ph-B-precursor ALL <p>PBAC Comment: Initial written authority was appropriate, with telephone authority for first and second continuation.</p> <p>The restriction should explicitly exclude patients with CNS disease.</p> <p>PBS subsidised blinatumomab should not be provided to inpatients.</p>	<ul style="list-style-type: none"> Minor changes. <p>Resubmission agreed.</p> <p>Proposed restriction explicitly excluded patients with CNS and testis disease.</p> <p>The resubmission reiterated the arguments in favour of PBS funding for inpatients.</p>
Requested price	<ul style="list-style-type: none"> Cost per vial: \$ [REDACTED] <p>Average cost per course of treatment: \$ [REDACTED] (use of 1 vial per day i.e. [REDACTED] vials for the average dose of [REDACTED] µg).</p>	<ul style="list-style-type: none"> Cost per vial: \$ [REDACTED] Confidential effective price of \$ [REDACTED] <p>Average cost per course of treatment: \$ [REDACTED] (efficient use of vials i.e. [REDACTED] vials for the average dose of [REDACTED] µg).</p>
Main comparator	<ul style="list-style-type: none"> SC <p>PBAC Comment: Comparator was appropriate.</p>	<ul style="list-style-type: none"> No change.
Clinical evidence	<ul style="list-style-type: none"> Two single-arm Phase II studies: MT103-211: pivotal study (n=225) MT103-206: dose-finding study (n=36) A retrospective historical control study (20120310) using SC (n=1,139) <p>PBAC Comment: No comment.</p>	<ul style="list-style-type: none"> No change.
Key effectiveness data	<ul style="list-style-type: none"> MT103-211: CR + CRh* = 43.9% (0.37, 0.51); OS = 6.4 months MT103-206: CR + CRh* = 69.4% (0.52, 0.84), OS = 9.8 months 20120310: CRsg = 24.0% (0.20, 0.27); OS = 3.3 months <p>PBAC Comment: The most informative analysis would be against the weighted post-2000 control data.</p> <p>Bone marrow blasts and platelet levels should be matched in the weighted comparison.</p>	<ul style="list-style-type: none"> No change. <p>The resubmission provided this data as a secondary analysis, using data from 1990-2013 as the key analysis for SC.</p> <p>Data was not available.</p>
Key safety data	<ul style="list-style-type: none"> No comparative safety analysis was provided <p>PBAC Comment: Comparative adverse event data from the TOWER trial would be informative for a robust assessment of comparative harms.</p> <p>Blinatumomab was associated with cytokine release syndrome which required access to non-conventional therapy and inpatient support.</p>	<ul style="list-style-type: none"> No change. <p>TOWER trial data was not yet available. CSR is expected late 2016, with early results presented mid-2016.</p> <p>Only 1/189 patients in MT103-211 received the investigational drug tocilizumab.</p>

Public Summary Document – July 2016 PBAC Meeting

<p>Clinical claim</p>	<ul style="list-style-type: none"> • Blinatumomab was superior in terms of both comparative effectiveness and safety over SC combination chemotherapies. <p>PBAC Comment: Clinical claim of superior efficacy was difficult to assess. Blinatumomab had clear efficacy in a minority of patients and appeared superior to current salvage therapy; however, the magnitude of improvement in long-term outcomes could not be readily determined.</p> <p>The claim of superior safety was difficult to assess. Toxicity would vary depending on the clinical state of a patient when treatment was commenced. No comparative safety outcomes were provided. The comparative adverse event data from the TOWER trial will be informative.</p>	<ul style="list-style-type: none"> • No change. Data from the TOWER trial are not yet available but are to be considered for a managed entry scheme. Preliminary data from TOWER trial were presented with the PSCR.
<p>Economic evaluation</p>	<ul style="list-style-type: none"> • Cost-utility model with a cost/QALY of \$75,000 – 105,000/QALY. <p>PBAC Comment: PBAC was supportive of expediting the listing of blinatumomab if the weighted post-2000 control data could be used to inform a revised economic evaluation.</p> <p>Without access to the comparative results from the TOWER trial, residual uncertainty in a revised model could be dealt with by adjusting the price to mitigate risk to the Commonwealth.</p> <p>More detailed input data on the costs of allogeneic HSCT, and evidence based estimates of life expectancy post-allogeneic HSCT would improve reliability of the model.</p> <p>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.</p> <p>The model assumed that patients who responded would do so immediately, which might not be appropriate.</p> <p>The cost of blinatumomab administration was likely to be underestimated, particularly with regards to the managing of adverse events.</p>	<ul style="list-style-type: none"> • Cost-utility model with a cost/QALY of \$45,000 – 75,000/QALY. <p>This was provided as a sensitivity analysis.</p> <p>A ■% price reduction per vial was presented.</p> <p>No further detail was provided.</p> <p>Sensitivity analyses were performed, with increased cost of subsequent salvage therapy and associated disutility.</p> <p>Arguments provided in the resubmission suggest this might be a reasonable assumption.</p> <p>The 1.3% of patients who experienced severe cytokine release syndrome events in MT103-211 were reclassified to spend one month in hospital for treatment.</p>
<p>Number of patients</p>	<ul style="list-style-type: none"> • Year 1: ■ patients; Year 5: ■ patients <p>PBAC Comment: Estimates of use were highly uncertain, but total numbers were likely to be small.</p>	<ul style="list-style-type: none"> • Year 1: ■ patients; Year 5: ■ patients

Public Summary Document – July 2016 PBAC Meeting

Estimated cost to PBS/RPBS	<ul style="list-style-type: none"> • \$ [redacted] in Year 5 • \$ [redacted] over the first 5 years of listing <p>PBAC Comment: Estimates of financial implications were highly uncertain.</p> <p>Inclusion of allogeneic HSCT costs to MBS and PBS.</p>	<ul style="list-style-type: none"> • \$ [redacted] in Year 5 • \$ [redacted] over the first 5 years of listing <p>A risk sharing arrangement was proposed.</p> <p>This was included.</p>
Managed entry scheme	<p>PBAC comment: PBAC was supportive of expediting the listing of blinatumomab with a managed access program or similar arrangement.</p> <p>The request to consider the rule of rescue was premature without more definitive evidence of rescue. Even then the rule of rescue would be difficult to justify unless a major difference in the rate of allogeneic HSCT was demonstrated. More definitive evidence may become available when the TOWER trial is complete.</p>	<p>A managed entry scheme proposal using the Phase III TOWER trial was presented.</p> <p>If doubling in allogeneic HSCT rate was demonstrated by TOWER trial, rule of rescue could be enacted and a price revision would occur.</p>
PBAC decision	<ul style="list-style-type: none"> • Reject. <p>PBAC comment: Rejected due to uncertainties in comparative clinical evidence and a high and uncertain ICER</p>	-

Source: Compiled during the evaluation

ALL = acute lymphoblastic leukaemia; CAR = chimeric antigen receptor; CNS = central nervous system; CR = complete remission; CRh* = complete remission with partial haematological recovery; CRsg = complete remission as per study definition; HSCT = haematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; Ph- = Philadelphia chromosome negative; QALY = quality-adjusted life year; SC = standard care

The redacted table shows that at year 5, the estimated net cost to the PBS would be less than \$10 million per year.

4 Clinical place for the proposed therapy

- 4.1 The resubmission proposed that blinatumomab be used in the treatment of relapsed or refractory Ph- B-precursor ALL patients. It was not requested for use as first-line treatment. This was appropriate. The ESC reiterated that the primary aim of relapsed ALL treatment is to induce and maintain remission and allow for an allogeneic HSCT, as HSCT is considered the only potential cure for relapsed ALL. The ESC considered that blinatumomab provides a “bridge” to enable some patients to undergo HSCT, with achieving complete remission (CR) being a crucial step before HSCT.
- 4.2 The ESC noted the previous recommendation by the PBAC from November 2015 which highlighted the clinical need for an effective treatment in this patient population.

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

5 Comparator

- 5.1 The comparator, standard care chemotherapy, including FLAG with or without anthracycline, high dose methotrexate in combination with pegylated-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents, and high-dose cytarabine (HiDAC) base chemotherapy, was the same as in the original submission and was accepted as appropriate by the PBAC.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with blinatumomab compared to chemotherapy including achieving remission quickly, being able to undergo successful stem cell transplant, spending fewer days in hospital during treatment, manageable adverse effects and improved quality of life.

Clinical trials

- 6.3 The resubmission was based on the same studies as the original submission – two single-arm Phase II studies assessing the efficacy of blinatumomab, and a retrospective historical control study:
- MT103-211: pivotal study, single-arm blinatumomab, N = 225;
 - MT103-206: dose-finding study, single-arm blinatumomab, N = 36; and
 - 20120310: retrospective historical control study, N = 1,139.
- 6.4 To enable a comparison of the population analysed in the historical control against the patients in the blinatumomab studies, outcomes of the historical control were weighted to match key prognostic characteristics including age, prior HSCT, and prior lines of treatment.
- 6.5 A randomised controlled, Phase III trial, the TOWER trial, comparing blinatumomab with standard care chemotherapy, was stopped early in January 2016 (the expected completion date was August 2016) as pre-defined stopping criteria had been met. The only available information at the time of evaluation was the trial protocol and the statistical analysis plan.

Table 2: Key features of the TOWER trial

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes	Used in MES?
TOWER	383	Phase III, R, OL Up to 19 months	Unknown	- Adult; - > 5% blasts in bone marrow; - Refractory disease; - Relapsed disease (1 st remission < 12 months; after 1 st salvage therapy; or at any time after allogeneic HSCT) - Received intensive combination chemotherapy - ECOG performance status ≤ 2	OS; CR/CRh*/CRi; allogeneic HSCT rate; 100 day mortality following HSCT	Yes

Source: Sections F.2.2.2-F.2.2.3, pp275-280 of the resubmission

CR = complete remission; CRh* = complete remission with partial haematological recovery; CRi = complete remission with incomplete haematological recovery; ECOG = Eastern Cooperative Oncology Group; HSCT = haematopoietic stem cell transplant; MES = managed entry scheme; OL = open-label; OS = overall survival; R = randomised

Comparative effectiveness

- 6.6 The key outcomes from the blinatumomab studies are summarised below. The resubmission also included a weighted comparison for the subgroup of patients diagnosed post-2000 from the historical control, Study 20120310. These subgroup results were not provided in such a way that they could be verified or evaluated.

Table 3: Key results from the non-randomised studies

CR + CRh* or CRsg	Population	Blinatumomab		SC	
		N	% (95% CI)	N	% (95% CI)
MT103-211	PAS	189	43.9% (37%, 51%)	-	-
	FAS	225	44.0% (37%, 51%)	-	-
MT103-206	FAS	36	69.4% (52%, 84%)	-	-
20120310 (weighted)	1990-2013	-	-	186	24% (20%, 27%)
	Subgroup of patients from any site with data post-2000	-	-	-	█% (█%, █%) ^a
Overall survival		N	Months (95% CI)	N	Months (95% CI)
MT103-211	PAS	189	6.4 (4.3, 7.7)	-	-
	FAS	225	6.5 (4.7, 7.7)	-	-
MT103-206	FAS	36	9.8 (8.5, 14.9)	-	-
20120310 (weighted)	1990-2013	-	-	1,112	3.3 (2.8, 3.6)
	Subgroup of patients from any site with data post-2000	-	-	-	█ (█, █) ^a
Allogeneic HSCT		N	% (95% CI)	N	% (95% CI)
MT103-211	PAS	189	27.5%	-	-
	FAS	225	26.7%	-	-
MT103-206	FAS	36	50.0%	-	-
20120310	1990-2013	-	-	808	18% (15%, 21%)

Source: Table 3 of the November 2015 blinatumomab PBAC public summary document; and Section B.6.1, p94, and Section C.5.3, pp181 and 183 of the resubmission

CI = confidence interval; CR = complete remission; CRh* = complete remission with partial haematological recovery; CRsg = complete remission per study group definition; FAS = full analysis set; HSCT = haematopoietic stem cell transplant; PAS = primary analysis set; PBAC = Pharmaceutical Benefits Advisory Committee; PSCR = Pre-Sub-Committee Response; SC = standard care

^a Data could not be verified

- 6.7 For the treatment of relapsed or refractory Ph- B-precursor ALL, it appeared that blinatumomab was more effective than standard care chemotherapy in terms of remission rates, allogeneic HSCT rates and overall survival. The historical control comparator was somewhat sensitive to weighted subgroup analyses.
- 6.8 The PSCR and pre-PBAC response provided preliminary efficacy results of the median overall survival for each arm in the TOWER trial.

Table 4: Overall survival results from the TOWER trial compared with base case

Arm	TOWER (95% CI)	Base case in submission (95% CI)	Post-2000 sensitivity analysis (95% CI)
Median OS blinatumomab	7.7 months (5.6, 9.6)	6.4 months (4.3, 7.7)	█ months (█, █)
Median OS SC chemotherapy	4.0 months (3.3, 4.3)	3.3 months (2.8, 3.6)	█ months (█, █)*
Incremental median OS	3.7 months	3.1 months	█ months
Stratified log-rank	p = 0.012	-	-
Hazard ratio	0.71 (0.55, 0.93)	-	-

Source: PSCR (p1) Table 1, and pre-PBAC response (p1) Table 1.
CI = confidence interval; OS = overall survival; SC = standard care

- 6.9 The ESC considered that, while these preliminary data indicate that blinatumomab is likely to be superior to chemotherapy, the most clinically relevant outcome is transplant rate and post-transplant survival, noting from Table 2 above that these are both outcome measures in the TOWER trial. The ESC noted the estimates of median overall survival with blinatumomab were relatively short (7.7 months in TOWER and 6.4 months in MT103-211) and this is inconsistent with the substantial survival

advantage anticipated in patients undergoing a successful allogeneic HSCT.

- 6.10 The ESC noted that post-transplant survival is highly dependent on a patient being appropriate for transplant, often defined in practice as patients with no minimal residual disease.
- 6.11 The ESC further considered that the results in the SC chemotherapy arm of the TOWER trial were most closely aligned to the post-2000 data and considered that the post-2000 data were therefore the most appropriate basis of a comparison in the absence of data from TOWER.

Comparative harms

- 6.12 The resubmission provided no (new) comparative safety data. In November 2015, the PBAC noted that blinatumomab is associated with the important major toxicity of cytokine release syndrome and this required access to non-conventional therapy and inpatient support.
- 6.13 The PSCR provided preliminary safety results for each arm in the TOWER trial.

Table 5: Safety results from TOWER trial

	Blinatumomab (N = 267) n (%)	SC chemotherapy (N = 109) n (%)
All treatment related emergent adverse events	()	()
≥ Grade 2	()	()
≥ Grade 3	()	()
≥ Grade 4	()	()

Source: PSCR (p2) Table 2
SC = standard care

- 6.14 The ESC noted that pre-treatment with dexamethasone appeared to reduce the risk of cytokine release syndrome by reducing cytokine concentration without adversely impacting T-cell activation or the cytotoxic potential of blinatumomab, while some patients with severe reactions may require treatment with tocilizumab.

Benefits/harms

- 6.15 A summary of the comparative benefits of blinatumomab versus standard care chemotherapy is presented below. Similar to the original submission, there were no comparative harms presented in the resubmission.

Table 6: Summary of comparative benefits for blinatumomab and standard care chemotherapy

	Blinatumomab	SC	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Blinatumomab	SC	
CR + CRh* (or CRsg), n						
MT103-211 (FAS)	99/225	-	-	44	-	-
MT103-206	25/36	-	-	69	-	-
20120310 (1990-2012)	-	NR ^b	-	-	24	-
20120310 (Sites with 2000+ data)	-	-	-	-	■	-
Total allogeneic HSCT rate, n						
MT103-211 (FAS)	60/225	-	-	27	-	-
MT103-206	18/36	-	-	50	-	-
20120310	-	NR ^b	-	-	18	-
Overall survival, median (months)	Blinatumomab	SC		Absolute difference	HR (95% CI)	
MT103-211 (FAS)	6.5 (4.7, 7.7)	-		-	-	
MT103-206	9.8 (8.5, 14.9)	-		-	-	
20120310 (1990-2012)	-	3.3 (2.8, 3.6)		-	-	
20120310 (Sites with 2000+ data)	-	■ (■, ■)		-	-	

Source: Table 5, p9 of the November 2015 blinatumomab PBAC public summary document; and Section B.6.1, p94, and Section C.5.3, pp181 and 183 of the resubmission

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; PBAC = Pharmaceutical Benefits Advisory Committee; RD = risk difference; RR = relative risk; SC = standard care

^a Median duration of follow-up: MT103-211 = 6.5 months; MT103-206 = 8.5 months

^b Results weighted to Study MT103-211 population; only patients with available endpoint data were included.

- 6.16 Based on a naïve indirect comparison with no common reference, the comparison of blinatumomab with standard care chemotherapy appeared to result in improved complete response, complete response with partial haematological recovery, allogeneic HSCT rates and overall survival. The magnitude of long-term efficacy could not be determined.

Clinical claim

- 6.17 The resubmission reiterated its previous claim, describing blinatumomab as superior in terms of comparative effectiveness and superior in terms of comparative safety over standard care chemotherapies.
- 6.18 As no new clinical evidence was provided for evaluation with the resubmission, the claim for superior efficacy in the current resubmission remained difficult to assess. The current resubmission stated that the early cessation of the TOWER trial, which was triggered by the finding of an overall survival benefit, gave substance to the claims of benefit made in the original submission. The PBAC accepted that this observation was supportive, but not definitive. Evaluation of the mature results of the TOWER trial is needed to reach a final conclusion. In particular, the submission did not attempt to resolve the PBAC concerns regarding uncertainty in long-term outcomes.
- 6.19 As the resubmission provided no comparative safety evidence, the claim for superior safety also remained difficult to assess. Toxicity might vary depending on the clinical state of a patient when treatment was commenced. Limited preliminary safety results from the TOWER trial were presented in the PSCR, and did suggest that while the overall adverse event rate was high, the proportion of patients experiencing grade 4

or higher toxicity was less with blinatumomab than for standard chemotherapy.

6.20 The PBAC considered that the claim of superior comparative effectiveness was reasonable in light of the preliminary results provided from the TOWER trial.

6.21 The PBAC considered that the claim of superior comparative safety was reasonable.

Economic analysis

6.22 Consistent with the November 2015 submission, the resubmission 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 that compared blinatumomab with standard care chemotherapy. A summary is presented below.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model versus 25 months in Study MT103-211 and 60 months in Study 20120310
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	█% for benefits and costs
Software package	Excel 2010 (v14)

Source: Compiled during the evaluation
QALY = quality-adjusted life year

6.23 The PBAC previously considered that the 20-year time horizon in the economic model was appropriate; however the ESC noted that 20-year survival is only plausible in patients who have a successful allogeneic HSCT, and therefore it is difficult to extrapolate the current data to 20 years without knowing the rate of successful transplant. Further, in the model, long-term survival is not linked to a successful allogeneic HSCT.

6.24 A number of variables used in the economic evaluation differed from the original submission. These are presented below.

Table 8: Changed variables in the economic evaluation

Variable	July 2016 resubmission	November 2015 submission
Number of blinatumomab vials used	█	█
Cost of blinatumomab	\$ █	\$ █
Blinatumomab cost per treatment	\$ █	\$ █
Inpatient use of R60A for blinatumomab patients	█	█
Inpatient use of R60B for blinatumomab patients	█	█
Cost of blinatumomab hospitalisation	\$ █	\$ █

Source: Compiled during the evaluation

6.25 The reduction in blinatumomab vials used from █ in the previous submission to █ in the resubmission was appropriate as it reflected efficient use of vials in the first cycle. In November 2015, the PBAC considered that the number of blinatumomab vials might be overestimated as the efficient use of vials in the first cycle was not

considered (paragraph 6.38, November 2015 Public Summary Document). This was not a key driver of the economic model.

- 6.26 The key drivers of the revised economic model again were time horizon, utility values and inpatient costs. Although utility values and inpatient costs were updated in the resubmission, they remained uncertain.

Table 9: 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	The model did not consider the utility of patients undergoing allogeneic HSCT, adverse events or the probability of relapse.	Low; favours blinatumomab
Inpatient costs	Blinatumomab = \$ [REDACTED] (included costs associated with cytokine release syndrome, but did not include costs associated with neurologic events, therefore likely to be an underestimate); SC = \$ [REDACTED].	High; favours blinatumomab

Source: Compiled during the evaluation
 HSCT = haematopoietic stem cell transplant; SC = standard care

- 6.27 The results of the stepped economic evaluation are presented in the table below.

Table 10: Results of the stepped economic evaluation

Step and component	Blinatumomab	Standard care	Increment
Step 1: Study-based costs and outcomes (2 year time horizon)			
Costs	\$ [REDACTED]	\$75,781	\$ [REDACTED]
Life years gained	[REDACTED]	0.50	[REDACTED]
Incremental cost/extra life year gained			\$ [REDACTED]
Step 2: Modelled evaluation (time horizon increased to 20 years)			
Costs	\$ [REDACTED]	\$75,781	\$ [REDACTED]
Life years gained	[REDACTED]	1.49	[REDACTED]
Incremental cost/extra life year gained			\$ [REDACTED]
Step 3: Modelled evaluation (discount rate of 5% applied)			
Costs	\$ [REDACTED]	\$75,781	\$ [REDACTED]
Life years gained	[REDACTED]	1.11	[REDACTED]
Incremental cost/extra life year gained			\$ [REDACTED]
Step 4: Modelled evaluation (additional costs included: HSCT, CR follow-up, palliative care)			
Costs	\$ [REDACTED]	\$123,456	\$ [REDACTED]
Life years gained	[REDACTED]	1.11	[REDACTED]
Incremental cost/extra life year gained			\$ [REDACTED]
Step 5: Modelled evaluation (average utility of 0.728 applied to 'before relapse' and 'after relapse' states)			
Costs	\$ [REDACTED]	\$123,456	\$ [REDACTED]
QALYs	[REDACTED]	0.81	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 6: Modelled evaluation (utility of 0.84 for 'before relapse' and 0.35 for 'after relapse' applied)			
Costs	\$ [REDACTED]	\$123,456	\$ [REDACTED]
QALYs	[REDACTED]	0.75	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Incremental cost/extra QALY gained – November 2015			\$ [REDACTED]

Source: Table D.5-2, p239 of the resubmission; and Blin_v_2_01.xlsm Excel workbook
 CR = complete remission; HSCT = haematopoietic stem cell transplant; QALY = quality-adjusted life year

- 6.28 The resubmission estimated incremental cost effectiveness ratios (ICER) of \$45,000 - \$75,000 per life year gained and of \$45,000 - \$75,000 per quality-adjusted life year (QALY) gained. In November 2015, the PBAC considered the original economic model unreliable for decision making. The results of the economic evaluation presented in the resubmission remained unreliable as a number of concerns raised by the PBAC were not addressed, including:
- the weighted analysis for patients diagnosed post-2000 from the historical control, Study 20120310, was not used to populate the standard care arm;
 - not all costs of toxicity due to treatment were included;
 - the cost and utility consequences for patients who received further salvage therapies were not considered;
 - more detailed input data on the costs of allogeneic HSCT were not provided; and
 - evidence based estimates of life expectancy post-allogeneic HSCT were not considered.
- 6.29 In the economic model, 40% of patients achieving CR are assumed to undergo an allogeneic HSCT. This resulted in 17.1% of patients treated with blinatumomab undergoing HSCT compared with 9.6% in the SC chemotherapy arm.
- 6.30 There were no changes to the number of life years or QALYs gained in the resubmission. The change in ICER was primarily due to the reduced cost of blinatumomab and the efficient use of vials.
- 6.31 The results of the economic evaluation using weighted historical control data from patients diagnosed post-2000 were presented as a sensitivity analysis.

Table 11: Results of the economic evaluation using weighted historical control data from patients diagnosed post-2000 in Study 20120310

	Δ cost	Δ QALYs	ICER
Base case – July 2016 resubmission	\$ [REDACTED]	0.93	\$ [REDACTED]
Base case – November 2015 submission	\$ [REDACTED]	0.93	\$ [REDACTED]
Using post-2000 patient data from Study 20120310	\$ [REDACTED]	0.73	\$ [REDACTED]

Source: Blin_v_2_01.xlsm Excel workbook

ICER = incremental cost-effectiveness ratio

- 6.32 The use of post-2000 patient data from Study 20120310 increased the ICER from \$45,000 - \$75,000/QALY to \$75,000 - \$105,000/QALY. Although post-2000 data was used to populate the standard care arm of the model, the ICER of \$75,000 - \$105,000/QALY remained unreliable and was likely to be optimistic as the issues surrounding costs of toxicity, costs of allogeneic HSCT and life expectancy post allogeneic HSCT were not addressed.

Drug cost/patient/treatment: \$ [REDACTED].

- 6.33 The resubmission estimated that the cost per blinatumomab treatment would be \$ [REDACTED], assuming an average total dose of [REDACTED] μ g ([REDACTED] cycles and [REDACTED] vials). The original submission estimated an average cost of treatment of \$ [REDACTED].
- 6.34 It may be appropriate to limit use to once per lifetime, as retreatment is not proven to be effective and not recommended in the National Comprehensive Cancer Network

guidelines. In the TOWER trial, patients could have more than five cycles of blinatumomab, but the proposed listing indicates a maximum of 5 cycles of therapy for PBS-subsidy.

- 6.35 The ESC considered it likely in practice that patients who are unable to receive a transplant may remain on blinatumomab maintenance therapy for longer than five cycles (the maximum number of cycles specified in the Product Information), increasing the drug cost per patient.

Estimated PBS usage & financial implications

- 6.36 This resubmission was not considered by DUSC. The resubmission used the same epidemiological approach to estimate the extent of use of blinatumomab and the financial implications to the PBS/RPBS and MBS as the original submission.
- 6.37 The estimates were updated to account for a 2.5% increase in the ALL incident population, the revised cost and the efficient use of vials. The resubmission included costs associated with allogeneic HSCT.

Table 12: Estimated use and financial implications of listing blinatumomab on the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	█	█	█	█	█
Vials ^a	█	█	█	█	█
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ █	\$ █	\$ █	\$ █	\$ █
November 2015 submission	\$ █	\$ █	\$ █	\$ █	\$ █

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

^a Assuming █ vials per treatment course

The redacted table shows that at year 5, the estimated number of patients would be less than 10,000 per year, and the net cost to the PBS would be less than \$10 million per year.

- 6.38 As per the original submission, the resubmission estimated the proportion of patients cured after first-line treatment (39%) and the proportion that had an initial response followed by relapse (50%) from Oriol (2010). These were not correctly estimated; using corrected calculations, the proportion of patients cured after first-line treatment was 44% and the proportion who had an initial response followed by relapse was 45%. These values were considered in a sensitivity analysis in the evaluation.
- 6.39 The ESC considered that financial estimates might be underestimated due to patients unfit for transplant remaining on prolonged blinatumomab maintenance therapy and receiving more than █ vials. Furthermore, the ESC noted the possibility of use beyond estimated numbers of patients into older teenagers treated outside of paediatric centres.

- 6.40 Despite the addition of some allogeneic HSCT costs, the usage and financial implication estimates remained uncertain, due to:
- Potential differences between the estimated number of patients with relapsed or refractory Ph- B-precursor ALL and the actual number of patients in the Australian population, particularly in the older adolescent and young adult age group; and
 - The assumption in the submission that the PBS would fund all inpatient blinatumomab.
- 6.41 The costs of allogeneic HSCT and its follow-up were not consistent between Sections D and E of the resubmission.

Table 13: Cost of allogeneic HSCT and follow-up treatment used in the resubmission

	Section D	Section E
Cost of allogeneic HSCT	\$96,336	\$78,202.28
Cost of follow-up	0-6 months: \$64,180 7-12 months: \$20,873 13-24 months: \$9,728 ≥ 25 months: \$ 1,944/year	\$1,944

Source: Compiled during evaluation
HSCT = haematopoietic stem cell transplant

- 6.42 The costs used in Section D of the resubmission for allogeneic HSCT and its follow up treatment were based on the UK Stem Cell Strategic Forum estimates. The total cost of allogeneic HSCT included: (i) the cost of pre-transplantation screening (6%; \$5,780); (ii) donor costs (26%; \$25,047); and (iii) the recipient's HSCT procedure (69%; \$66,186). In Section E, the cost of allogeneic HSCT was based on the AR-DRG cost for allogeneic transplant in patients older than 17 years (\$78,202). The resubmission stated that this cost was similar to the UK cost of procedure. The cost of follow up treatment in Section E (\$1,944) was the cost to the PBS of outpatient cyclosporin (2 x 50 mg capsules daily). When compared to Section D, the costs used in Section E might have been underestimated.
- 6.43 The PBAC previously considered that the original usage and financial estimates were highly uncertain, and that total numbers were expected to be small. The estimates in the resubmission remained uncertain.

Quality Use of Medicines

- 6.44 The resubmission raised equity and quality use of medicine issues surrounding the proposal that blinatumomab be PBS reimbursed for hospital inpatients. The ESC considered that the submission did not provide any additional information to fundamentally change the previous PBAC view related to the precedent for inpatient reimbursement of PBS medicines.
- 6.45 With regards to equity, the resubmission suggested that:
- the processes by which high cost drugs are funded in hospitals is not universal; therefore, it cannot be assumed that all blinatumomab applications would be approved; and

- hospitals that are referral centres for ALL patients would have multiple patients attempting to secure blinatumomab funding. As hospital budgets are finite, it could be possible that some patients would not be funded.

6.46 The resubmission raised the following quality use of medicine issues:

- should inpatient blinatumomab supply not be PBS reimbursed, patients might be discharged sooner than is optimal to secure the PBS reimbursed component of therapy; and
- minimising the expense of inpatient blinatumomab might present an opportunity for hospitals looking for efficiency gains.

Financial Management – Risk Sharing Arrangements

6.47 The resubmission presented a Risk Sharing Arrangement and a managed entry scheme.

6.48 In order to reduce financial uncertainty for the PBS/RPBS, the resubmission proposed a financial cap set at 120% of the estimated blinatumomab **eligible** population, rather than the **treated** population. Any use beyond the cap would receive a rebate of ■%. The cap would be set at an agreed estimate of average number of vials per eligible patient.

Table 14: Proposed patient number and financial caps for blinatumomab

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients treated with blinatumomab	■	■	■	■	■
Cost of blinatumomab to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Blinatumomab eligible patients	■	■	■	■	■
Number of patients at which the cap would be set	■	■	■	■	■
Number of vials used (assuming ■ vials per patient)	■	■	■	■	■
Financial cap	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table F.2-1, p274 of the resubmission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

6.49 The ESC advised that an alternative risk-share cap with a 100% rebate of any cost beyond the estimate of treated patients receiving ■ vials per patient could help manage the financial risk of patients remaining on prolonged blinatumomab maintenance therapy, and the possibility of use beyond the estimated number of patients to older teenagers.

Possible alternative approach to PBS listing

6.50 The proposed managed entry scheme aimed to address the clinical uncertainty surrounding the efficacy of blinatumomab and standard care chemotherapy, and the rate of allogeneic HSCT.

- 6.51 The resubmission proposed that overall survival data from the TOWER trial should be used to populate the economic model and determine a price of blinatumomab, using the fixed ICER of \$45,000/QALY – \$75,000/QALY. This was the base case ICER calculated in the resubmission, using all patients in the historical control to populate the standard care arm.
- 6.52 The ESC considered that it is likely that data from the TOWER trial would reduce uncertainty in the economic model, as it would provide a more robust assessment of blinatumomab versus standard care chemotherapy and of allogeneic HSCT rates. However, without full evaluation, it would be difficult to assess the applicability of the TOWER trial to the Australian population, the reliability of the results and the suitability of the results to populate the economic model. Given the early termination of the TOWER trial, it was also unlikely that this trial would provide adequate longer-term data for a modelled assessment of benefits and harms.
- 6.53 In November 2015, the PBAC considered the economic model was likely to be optimistic and unreliable for decision-making. As the resubmission did not address all the concerns raised by the PBAC, the economic model remained unreliable and it might not be valid to use the model to determine the blinatumomab price. The ESC considered it unlikely that the incorporation of the TOWER trial results into the existing model would be informative.
- 6.54 Additionally, the resubmission requested that if the proportion of patients undergoing an allogeneic HSCT in the blinatumomab arm in TOWER was more than double the proportion in the standard care chemotherapy arm, the rule of rescue could be enacted. The resubmission interpreted this to mean that the ICER could be increased to between \$75,000 and \$105,000, and then the price of blinatumomab determined.
- 6.55 The ESC suggested that the PBAC may wish to consider an alternative pragmatic approach to address the clinical uncertainty for a PBS listing given the small eligible patient population, the clinical need for more effective treatment for relapsed ALL and the uncertainty surrounding the use of TOWER trial results in the existing economic model.
- 6.56 The ESC suggested that this alternative approach might take the form of an initial PBS-listing based on the parameters of the existing economic model, with a review of this listing after a period of two years based on the rate of successful transplants across all patients treated with PBS-subsidised blinatumomab. The ESC noted that post-transplant survival is predictable soon after transplant, and that a two year review period would be clinically appropriate, depending on the rate of accrual of patients starting PBS-subsidised blinatumomab and PBAC's advice on a reasonable sample size. The percentages of patients achieving and then surviving transplant could be compared to the corresponding estimates from the TOWER trial. The observed percentages could be used in place of the TOWER-based percentages, and, if necessary, the price of blinatumomab reduced to achieve the same ICER. Consistent with similar existing arrangements, any price reduction would become the basis for rebating the extra cost of PBS-subsidised blinatumomab, together with the appropriate rate of interest.

- 6.57 The ESC noted that such an arrangement would require a willingness from the sponsor to fund the collection of data on HSCT rates to inform the effectiveness and ongoing cost-effectiveness of blinatumomab.
- 6.58 Consistent with similar existing arrangements, the ESC further noted that possible outcomes following collection of patient survival data could be that the price of blinatumomab may reduce, or that blinatumomab may be removed from the PBS, and noted that the management of all potential outcomes was a relevant consideration for the PBAC. For this reason, a note about these arrangements would need to be included in any PBS listing.
- 6.59 The PBAC considered that a managed entry scheme (MES), modified from that proposed in the resubmission and from that suggested by the ESC, would be appropriate to address the primary uncertainty over the incremental proportion of patients alive two years after starting blinatumomab or current standard care therapy, while providing early access to those patients for whom there is a high clinical need. The PBAC noted that its recommendation to list initially was based on an ICER/QALY of \$45,000 – 75,000. If the modelled survival holds true at the completion of any MES in the future, then this initial ICER is deemed to be of acceptable cost effectiveness. The PBAC considered that a MES for blinatumomab should be guided by the following conditions.
- 6.60 The initial price for blinatumomab in the MES would be established based on respecifying the base case of the submitted model to use only the weighted historical control data from patients diagnosed post-2000 for the comparator, which estimated an incremental QALYs gained of 0.73. The PBAC recommended this respecification to reflect more recent clinical management given that the model relied on a non-randomised comparison, and noted that it would be possible to back-calculate the blinatumomab price needed to make this model generate an ICER/QALY of \$45,000 – \$75,000. The PBAC noted that the back-calculation resulted in a reduction of the effective dispensed price from \$ [REDACTED] to \$ [REDACTED].
- 6.61 The possible outcomes following completion of the MES would be that either:
- the price of blinatumomab would reduce; or
 - the price of blinatumomab would be maintained.
- 6.62 Entering into a MES places the financial burden on the Commonwealth for the upfront risk associated with the uncertain clinical benefit of blinatumomab. Accordingly, should the incremental proportion of patients alive two years (or 25 months, whichever is easiest for including in the model and/or obtaining from the trial) after starting blinatumomab or current standard care therapy be smaller in the TOWER results than modelled from the non-randomised comparison, then the sponsor would rebate the Commonwealth taking account of the following:
- the price reduction of blinatumomab would be calculated to maintain the current ICER (\$45,000 – \$75,000) with reduced clinical benefits
 - the rebate would be calculated by multiplying this price reduction by the number of PBS-dispensed prescriptions of blinatumomab between the date of listing and the date of implementation of the price reduction, after applying an interest rate deemed appropriate by the Commonwealth.

- 6.63 The PBAC recommended that the ongoing randomised trial (TOWER) be the source of evidence to address this uncertainty, noting the intention to continue following remaining trial participants for at least two years (or 25 months). The PBAC anticipated that the results of this trial should become available with sufficient time to resubmit the revised model within two years.
- 6.64 The submission to complete the MES should be provided as soon as possible after sufficient follow-up of the TOWER trial to be confident of the incremental overall survival after a majority of participants remaining alive have been followed beyond two years (or 25 months). In order to finalise the MES, the sponsor should be required to confirm that sufficient follow-up is intended, including by specifying the schedule of analysing overall survival from TOWER following the initial results presented in Table 4.
- 6.65 The PBAC recommended that at the conclusion of the MES, the submission should provide the further follow-up of TOWER. Specifically, the individual patient data (IPD) based analysis of overall survival, using the standard graphics of Kaplan-Meier curves, together with standard reporting of these results (log rank p-values, hazard ratios with 95% confidence intervals, medians, difference in medians, etc.).
- 6.66 The PBAC recommended that the overall survival results of this trial be used according to the intent-to-treat analysis, ie without adjustment or censoring for any cross-over to other therapies following cessation of the initial randomised therapy. The PBAC advised that, although this might bias the consequently modelled economic evaluation against blinatumomab, this was necessary to address the primary uncertainty of the model. The PBAC also considered that this particular recommendation should be considered in the light of other recommendations below relating to the model that would be biased in favour of blinatumomab.
- 6.67 The PBAC recommended that the resubmitted modelled economic evaluation should:
- estimate the incremental overall survival for the two arms of the model up to two years based directly on the observed overall survival Kaplan-Meier curves (intent-to-treat analysis)
 - estimate the incremental proportion of patients alive at two years (or 25 months) across the two Kaplan-Meier curves from the clinical evaluation
 - then, for simplicity, allow extrapolation modelling on both arms for the overall survival curves from this time point, whereby patients still alive at two years (or 25 months) have normal life expectancy for the remainder of the 20-year model, because the extrapolation curves at two years (or 25 months) might start from different proportions remaining alive than in the current model. Although this largely reflects the extrapolation basis in the model it is biased in favour of blinatumomab because the current model's 2 to 5 year extrapolations result in greater convergence of the overall survival curves.
- 6.68 The PBAC recommended that the other inputs to the model should not change for the resubmission, despite the fact that the associated biases are in favour of blinatumomab. These include:
- costing blinatumomab based on an average of ■ vials (■ cycles) because this is consistent with the recommended PBS restriction of a maximum of 5 cycles. The actual average number of vials used in TOWER is likely to be higher

- (reflecting use beyond 5 cycles) and in this case the outcomes (including overall survival) will be reflective of longer use of blinatumomab
- accepting that the difference in proportion alive at two years (or 25 months) essentially means a difference in the proportions of cured patients
 - not censoring for transplant, as this is central to the proposed listing
- 6.69 The PBAC emphasised that the primary purpose of keeping other aspects of the model constant between the version forming the basis for this initial recommendation and the version to be provided at the end of the MES was to examine the consequence of any change in the estimate of the identified primary uncertainty.
- 6.70 The PBAC indicated that any other unexpected but relevant developments emerging before completion of the MES, such as unexpected safety signals or any grounds to cast doubt on the assumption of cure, would then be considered according to usual PBAC processes. Such developments may be reported by the sponsor or raised by the PBAC and, if substantial, may modify the PBAC recommendations arising from the review of the MES.
- 6.71 The MES arrangements for blinatumomab would need to be formalised in any Deed of Agreement established for the purposes of PBS listing, including confirmation from the sponsor that overall survival results after a majority of participants remaining alive have been followed in TOWER beyond two years (or 25 months) would be available. The PBAC recommended that the Department adopt its standard approach in finalising this Deed to minimise the risk of any unreasonable delay in completing the MES, such as imposing a suitable price reduction in the event of such a delay.
- 6.72 The nature of these MES arrangements (without details of the consequences for pricing) should be made public, particularly to inform patients, prescribers and other sponsors of their existence and any other possible consequences.
- 6.73 The PBAC recommended that the Risk-Sharing Arrangements be kept separate from the MES arrangements in the proposed Deed of Agreement.
- 6.74 The PBAC recommended that the expenditure caps reflect the estimate of ■ vials (■ cycles) as proposed because this is consistent with the requested upper limit of 5 cycles of blinatumomab therapy, but that the caps should reflect the estimated treated population (■ to ■ adults) rather than the proposed 120% of the estimated eligible population (■ to ■ adults). The PBAC noted that including the duration of therapy administered whilst every patient is in the inpatient setting provided sufficient sharing of the risk of uncertainty without also increasing the estimated number of patients as proposed by the sponsor.
- 6.75 The PBAC recommended that a 100% rebate to the Commonwealth should apply beyond the corresponding expenditure caps.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of blinatumomab for the

treatment of relapsed or refractory Ph- B-precursor acute lymphocytic leukaemia (ALL) on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy).

- 7.2 The PBAC recalled that in November 2015, it did not recommended listing of blinatumomab on the basis of uncertainties in comparative clinical effectiveness and a high and uncertain ICER. In the current resubmission, the PBAC considered that preliminary data from the TOWER trial provided the Committee with more confidence that blinatumomab has benefits in OS compared to standard care chemotherapy, and noting the high clinical need and importance of early access to treatment for this patient population, as reflected in consumer input, recommended listing under a Managed Entry Scheme (MES). The PBAC was satisfied that blinatumomab provides, for some patients, a significant improvement in efficacy and reduction in toxicity over standard care chemotherapy; however the size of the incremental treatment effect is still uncertain. This uncertainty is the basis of the MES.
- 7.3 The PBAC considered the secretariat suggested restriction was appropriate. As the majority of patients in the Phase II studies received less than two treatment cycles, likely due to early success or treatment failure, the PBAC considered it appropriate that the restriction limits use to a maximum of 5 cycles of blinatumomab. The PBAC agreed that the restriction should remain silent on age, noting that most paediatric patients up to 16 years of age are already being treated appropriately through clinical trials.
- 7.4 The PBAC reiterated that PBS subsidised blinatumomab should not be provided to public hospital inpatients, and therefore that the maximum quantities and repeats as suggested by the Secretariat were appropriate for the public hospital listing to account for the first 9 days of cycle 1 and the first 2 days of cycle 2 being provided to inpatients. This will result in the public and private hospital listings having different numbers of repeats. This arrangement avoids a precedent for PBS funding of inpatient chemotherapy in public hospitals.
- 7.5 The comparator, standard care chemotherapies, was unchanged from the previous submission and remained appropriate.
- 7.6 In making its recommendation, the PBAC considered that data from the two single-arm Phase II studies compared to a retrospective historical control presented were reassuring, however the extent of overall survival benefit remains unclear. The PBAC maintained that the weighted post-2000s data from the historical control are the most appropriate basis for an analysis of comparative efficacy in the absence of mature data from TOWER, noting that these data were provided in the resubmission but were presented such that they were not able to be verified or evaluated. The preliminary results from the TOWER trial presented in the PSCR provide reassurances that evidence that is more robust will be forthcoming in the foreseeable future to better inform the clinical effectiveness and cost effectiveness. The PBAC has proposed a plan to review this evidence as soon as it becomes available to ensure patients receiving medicines on the PBS are being treated according to the best available evidence and that the cost of the treatment remains justified in terms of acceptable cost-effectiveness. Should the modelled extent of benefits not be realised, the Committee has recommended measures to minimise the risk of unjustified health care expenditure.

- 7.7 The PBAC considered that the preliminary TOWER trial results provided by the sponsor in the PSCR indicated the likely superiority in efficacy of blinatumomab over standard care chemotherapy. However, the PBAC disagreed with the ESC that the most clinically relevant outcome is transplant rate and post-transplant survival, instead considering that overall survival was the most relevant outcome to inform decision-making.
- 7.8 The PBAC considered that the preliminary safety results from TOWER indicate that blinatumomab is likely to be superior in terms of comparative safety compared to standard care chemotherapy, and agreed that the mature TOWER results would provide the PBAC with increased confidence in the safety claim.
- 7.9 The PBAC accepted the structure of the economic model, acknowledging that the ICER may be optimistic, and reiterating that the preferred input into the economic model is the comparative results from the TOWER trial. The PBAC noted that a key driver of the model is the absolute difference in survival at two years (or 25 months), where the extrapolation of the modelled curves largely plateau consistent with the likely progression of the disease. The magnitude of this difference at two years (or 25 months) will be confirmed with mature data from the TOWER trial. The PBAC considered that the base case ICER of \$45,000 – \$75,000/QALY was high but acceptable in this patient population.
- 7.10 The PBAC noted that the estimated number of adult patients treated with blinatumomab as presented in the resubmission was reasonable.
- 7.11 The PBAC considered that the rule of rescue does not apply to blinatumomab as an alternative therapy exists, and because blinatumomab is not in itself a cure.
- 7.12 The PBAC recommended that blinatumomab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.13 The PBAC advised that blinatumomab is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Early Supply Rule should not apply.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it has received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 To be finalised.

9 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.

10 Sponsor's Comment

Amgen are pleased with the PBAC's recommendation and recognition of the clinical need for an effective treatment in this patient population. Amgen are committed to working with the PBAC to achieve a PBS listing for blinatumomab at the earliest opportunity, but also need to ensure that any arrangements are sustainable to enable patients to benefit from blinatumomab both now and in the future.