

7.13 BLINATUMOMAB

Powder for I.V. infusion 38.5 micrograms, Blincyto[®], Amgen

1 Purpose of Application

- 1.1 The minor resubmission requested Section 100 Authority Required (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) in haematological complete remission with minimal residual disease (MRD) following induction chemotherapy.
- 1.2 The minor resubmission aimed to address issues raised by the PBAC in its March 2019 deferral of blinatumomab for this indication.

2 Requested listing

- 2.1 The requested restriction was unchanged from the March 2019 resubmission except for the following amendments which were previously proposed by the Secretariat:
- Changed the number of repeats in each setting from 3 to 1 (consistent with July 2018 blinatumomab PBAC Minutes, paragraph 2.3);
 - Included the criteria ‘Patient must have achieved a complete remission’ in the initial restriction’; and
 - Included a criteria specifying that MRD must be measured using polymerase chain reaction or flow cytometry (consistent with March 2019 blinatumomab PBAC Minutes, paragraph 2.6).
- 2.2 The requested restriction is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with a strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
BLINATUMOMAB 38.5 µg, injection, 1 vial	784	1	<u>Published:</u> \$81,418 (public) \$82,595.98 (private) <u>Effective^a:</u> \$ [REDACTED] (public) \$ [REDACTED] (private)	Blincyto®	Amgen Australia Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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
Condition:	Acute lymphoblastic leukaemia (ALL)

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PBS Indication:	Minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (B-ALL) in patients with complete haematological remission
Treatment phase:	Initial treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>The condition must be B-cell precursor acute lymphoblastic leukaemia with an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2,</p> <p>AND</p> <p>The condition must not be present in the central nervous system or testis,</p> <p>AND</p> <p>Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy,</p> <p>AND</p> <p>Patient must have achieved a complete remission,</p> <p>AND</p> <p>Patient must have MRD defined as at least 10^{-4} (0.01%) blasts based on measurement in bone marrow, documented after an interval of at least 2 weeks from last systemic chemotherapy,</p> <p>AND</p> <p>Minimal residual disease must be measured using polymerase chain reaction or flow cytometry,</p> <p>AND</p> <p>The treatment must not be more than two treatment cycles under this restriction in a lifetime.</p>

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<p>Prescriber Instructions:</p>	<p>According to the TGA-approved Product Information, hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a health care professional or hospitalisation is recommended.</p> <p>An amount of 784 micrograms will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.</p> <p>Blinatumomab is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form;</p> <p>(2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and</p> <p>(3) a signed patient acknowledgement.</p> <p>(4) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage;</p> <p>(5) a copy of the most recent bone marrow biopsy report of no more than one month old at the time of application.</p> <p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time when an assessment is required must cease PBS-subsidised therapy with this agent.</p>
<p>Administrative Advice:</p>	<p>A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and ANC of greater than 1,000 per microliter.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
<p>Cautions:</p>	<p>Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.</p>

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^a Calculated based on: effective price (\$ [REDACTED] per vial) = published price – rebate.

Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	<p>Patient must have previously received PBS-subsidised initial treatment with this drug for this condition,</p> <p>AND</p> <p>Patient must have achieved a complete remission,</p> <p>AND</p> <p>Patient must be minimal residual disease negative defined as either undetectable using the same assay as used to determine original eligibility or less than 10⁻⁴ (0.01%) blasts based on measurement in bone marrow,</p> <p>AND</p> <p>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>The treatment must not be more than two treatment cycles under this restriction in a lifetime.</p>
Prescriber instructions:	Per initial restriction
Administrative Advice:	<p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time when an assessment is required must cease PBS-subsidised therapy with this agent.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Special Pricing Arrangements apply.</p>
Cautions:	Per initial restriction

2.3 The pre-PBAC Response requested that the PBAC consider whether next generation sequencing could be included in the restriction as an additional means to identify eligible patients noting that some centres are developing next generation sequencing technology to test for MRD.

2.4 The resubmission proposed increasing the special pricing arrangement rebate from ██████% as proposed in the previous submission (which is the rebate that currently applies in the relapsed/refractory (R/R) setting), to ██████%. The increased rebate was proposed to apply to the requested blinatumomab listing only (i.e. only in the MRD setting). In the sponsor’s March 2019 pre-PBAC response, a ██████% rebate was proposed to apply to both the requested MRD listing and the existing blinatumomab listing in the R/R setting (the differing rebates between the current resubmission and the March 2019 pre-PBAC response had only a minor impact on the total financial cost to the PBS, as discussed in Paragraph 4.17).

Proposed flow-on change to listing in the R/R setting

2.5 In March 2019, the PBAC considered it would be clinically appropriate to allow retreatment with blinatumomab in the R/R setting for patients who responded in the MRD setting. The PBAC further advised that an adequate response to blinatumomab in the MRD setting would constitute a relapse free period of at least 6 months following completion of blinatumomab treatment (March 2019 blinatumomab PBAC Minutes, paragraph 7.4).

2.6 As such, the resubmission’s suggested changes to the existing blinatumomab listing in the R/R setting are underlined. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. The changes have been applied to the listing recommended at the May 2019 intra-cycle PBAC meeting, in which the restriction was expanded to allow use in patients whose condition is Philadelphia chromosome positive (Ph+).

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Category / Program:	Section 100 – Efficient Funding of Chemotherapy
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
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – In Writing
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase	Induction treatment
Clinical criteria	The condition must be relapsed or refractory B-precursor cell ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, AND The condition must not be present in the central nervous system or testis, AND

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	<p>Patient must have previously received a tyrosine kinase inhibitor if the condition is Philadelphia chromosome positive,</p> <p>AND</p> <p>Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy,</p> <p>AND</p> <p>Patient must not have received more than 1 line of salvage therapy,</p> <p>AND</p> <p><u>Patient must not have received blinatumomab <i>previously for the treatment of minimal residual disease</i> OR</u></p> <p><u>Patient must have had a relapse-free period of at least six months following completion of treatment with blinatumomab for minimal residual disease.</u></p> <p>AND</p> <p>The condition must have more than 5% blasts in bone marrow,</p> <p>AND</p> <p>The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.</p>
<p>Prescriber Instructions:</p>	<p>According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a health care professional or hospitalisation is recommended.</p> <p>An amount of 651 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 1. An amount of 784 microgram, which may be obtained under Induction treatment - balance of supply restriction, will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 2.</p> <p>Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form;</p> <p>(2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form;</p> <p>(3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage;</p> <p><u>(4) If applicable, the date of completion of blinatumomab treatment for minimal residual disease and the date of the patient's subsequent relapse; and</u></p> <p>(5) a copy of the most recent bone marrow biopsy report of no more than one month old at the time of application.</p>
<p>Administrative Advice:</p>	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

	<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
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2.7 The PBAC noted that the intent of the change to the R/R listing is to allow patients who responded well to blinatumomab in the MRD setting to receive another course of blinatumomab in the R/R setting i.e. it is not intended to allow patients to access two courses of blinatumomab in the R/R setting.

2.8 The pre-PBAC Response stated that the sponsor agreed to the changes to the proposed MRD restriction and existing relapse/refractory restriction.

For more detail on PBAC’s view, see section 5 PBAC outcome.

3 Background

3.1 The PBAC has considered two previous submissions for blinatumomab for the treatment of patients in haematological complete remission with MRD following induction chemotherapy (July 2018 and March 2019).

3.2 The March 2019 submission was deferred to request further information from the sponsor on issues around the estimated incremental cost-effectiveness ratio (ICER), overall net financial implications, and proposed Risk Share Arrangement (RSA). In March 2019, the PBAC considered that the ICER was high, uncertain and likely underestimated. The PBAC considered that blinatumomab would only be cost-effective if the price was reduced and financial arrangements were put in place to ensure that savings due to reduced use of blinatumomab in the R/R setting would be realised (March 2019 blinatumomab PBAC Minutes, paragraph 7.1).

3.3 A summary of the outstanding matters of concern from the March 2019 consideration are provided in the table below.

Table 1: Summary of key outstanding matters of concern

	Matter of concern from March 2019	How the resubmission addressed it
Requested price	Submission: ██████% rebate for MRD indication Pre-PBAC response: ██████% rebate for both MRD and R/R indications	██████% rebate for MRD indication only

	Matter of concern from March 2019	How the resubmission addressed it
Economic evaluation	The PBAC considered there were significant uncertainties with the economic model and underpinning clinical data that likely overestimated the ICER. Base case ICER = \$75,000-\$105,000/QALY (with pre-PBAC response rebate = \$75,000-\$105,000). PBAC considered the ICER in the MRD setting should be < \$45,000 - \$75,000/QALY (the ICER accepted in the R/R setting). (Para 7.15)	ICER = \$45,000-\$75,000/QALY. (The only change to the economic model was the increased rebate)
Overall financial impact / RSA	Pre-PBAC response estimated there would be a ■% reduction in blinatumomab use in R/R setting if blinatumomab is listed for MRD. PBAC requested further information to justify these estimates.	Further information provided. Resulted in a ■% reduction in use in the R/R setting in Years 2 to 6. The Pre-PBAC response proposed a ■% reduction in the R/R setting in Years 2 to 6.

Source: Compiled during preparation of the Minor Overview, based on p1, Minor resubmission.
Paragraph references refer to the March 2019 blinatumomab PBAC Minutes.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Clinical trials

- 4.1 As a minor resubmission, no new clinical trials were presented.
- 4.2 The March 2019 submission was based on a propensity score indirect analysis of one single arm blinatumomab study (BLAST; n=116) and one retrospective historical cohort study of patients receiving treatment with standard of care chemotherapy (Study 20120148; N=287) in patients with B-ALL in haematological remission with MRD.

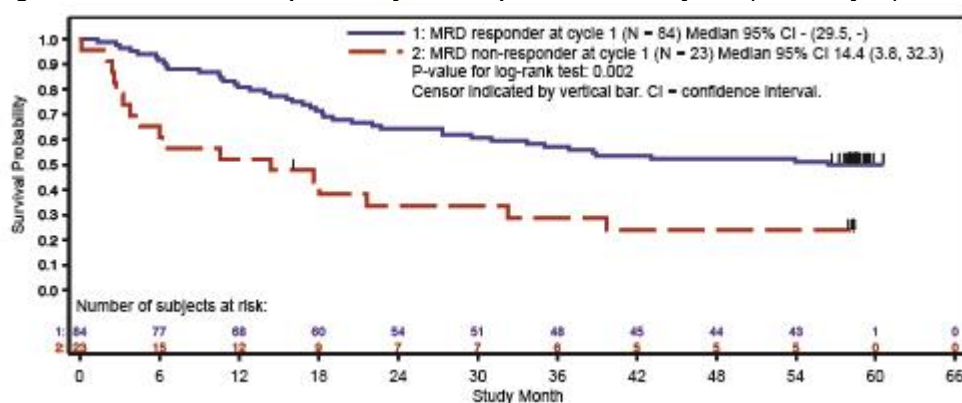
Comparative effectiveness

Relevant excerpts from March 2019 blinatumomab PBAC Minutes:

- 4.3 The PBAC noted that the PSCR provided updated survival data from the single-arm BLAST study that showed a median overall survival of 36.5 months (95% CI 22.0, not estimable) with a median follow up of 4.5 years (March 2019 blinatumomab PBAC Minutes, paragraph 7.9)
- 4.4 The PBAC considered that these updated data provided a clearer indication that blinatumomab may be associated with an overall survival advantage. However, the PBAC considered that it remained unclear whether blinatumomab would lead to long-term gains in overall survival given the lack of reliable comparative data and the relative immaturity of data from the BLAST study (March 2019 blinatumomab PBAC Minutes, paragraph 7.9)

4.5 The pre-PBAC Response noted that 5 year follow-up data from the final analysis of overall survival in the BLAST study (Gokbuget et al., 2019) was recently presented at the European Haematology Association congress in June 2019. With a median follow up of 59.8 months, the median overall survival was 36.5 months (95% CI: 22.0-not estimable). More than half of patients who achieved a complete MRD response following the first cycle of blinatumomab were alive at five years. The results of the final analysis are shown in Figure 1 below.

Figure 1: Overall survival in patients by MRD response status in Cycle 1 (final analysis)



Source: Gokbuget et al, Blinatumomab for minimal residual disease (MRD) in adults with B-cell precursor acute lymphoblastic leukemia (BCP-ALL): Median overall survival (OS) not reached at 5 years for complete MRD responders. EHA Library. 267373; S1619.

Sponsor hearing

4.6 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical claim

Relevant excerpts from March 2019 blinatumomab PBAC Minutes:

- 4.8 The PBAC previously considered that blinatumomab is effective in eliminating MRD and is associated with durable relapse-free survival and therefore, considered the claim of superior comparative effectiveness was adequately supported (March 2019 blinatumomab PBAC Minutes, paragraph 6.43).
- 4.9 The PBAC previously considered that the claim of non-inferior comparative safety was not adequately supported by the data (March 2019 blinatumomab PBAC Minutes, paragraph 6.44).

- 4.10 No changes were proposed to the clinical claim compared with the March 2019 resubmission which described blinatumomab as superior in terms of effectiveness versus standard of care chemotherapy (post induction consolidation) and non-inferior in terms of safety.

Economic analysis

Relevant excerpts from March 2019 blinatumomab PBAC Minutes:

- 4.11 In March 2019, the PBAC considered there were a number of issues with the economic model, including that haematopoietic stem cell transplant (HSCT) was not included as a health state and the model did not adequately reflect the different treatment pathways that patients treated with blinatumomab would undergo. Further, the PBAC considered that the model was uncertain because: it relied on an overall survival benefit that was uncertain; there were applicability issues with the clinical data; the disease management costs were likely to have been significantly overestimated in the consolidation chemotherapy arm; there were structural uncertainties; and the utility estimates were not adequately justified and unlikely to have been conservative (March 2019 blinatumomab PBAC Minutes, paragraphs 7.12-7.13). However, the PBAC acknowledged that no further comparative data were likely to be forthcoming and there was unlikely to be sufficient information to construct an economic model that would reliably model the condition (March 2019 blinatumomab PBAC Minutes, paragraph 7.1).
- 4.12 “The PBAC recalled that blinatumomab was previously recommended in the R/R setting at an ICER of around \$73,000/QALY, which was based on a model informed by comparative data from a randomised controlled trial (TOWER). Noting the significant uncertainties with the clinical data and economic model that [were unlikely to be conservative], the PBAC advised that the ICER in the MRD setting should not exceed that accepted in the R/R setting. Thus, the PBAC considered that a price reduction that results in an ICER less than \$73,000/QALY would be required.” (March 2019 blinatumomab PBAC Minutes, paragraph 7.15).

4.13 The only change to the economic evaluation presented in the March 2019 submission was the application of the proposed [REDACTED] % rebate. The results of the economic evaluation are presented below.

Table 2: Results of the economic evaluation

Type of resource item	Blinatumomab	Consolidation chemotherapy	Incremental difference
Costs	\$ [REDACTED]	\$283,978	\$ [REDACTED]
Life years	5.99	4.70	1.29
QALYs	4.80	3.60	1.19
Incremental cost per QALY gained			\$ [REDACTED]
Previous submission March 2019: pre-PBAC response ([REDACTED] % rebate)			\$ [REDACTED]
Previous submission March 2019: submission ([REDACTED] % rebate)			\$ [REDACTED]

Abbreviations: QALYs, quality adjusted life years

Source: BlinMRD_Sect3model_Apr19 Excel workbook of the resubmission and Table 13 of the March 2019 blinatumomab Minutes

4.14 With the [REDACTED] % rebate proposed, the ICER reduced to \$45,000/QALY - \$75,000/QALY. This aligned with the PBAC’s previous advice that a price reduction that results in an ICER less than \$45,000/QALY - \$75,000/QALY would be required (March 2019 blinatumomab PBAC Minutes, paragraph 7.15).

Drug cost/patient/course

4.15 The minor resubmission estimated that the drug cost of blinatumomab per patient per course was \$ [REDACTED]. This was based on 53 treatment days using the effective price of \$ [REDACTED] per vial per day; weighted between the private setting (41%) and public hospital use (59%). This is a decrease compared to: the March 2019 pre-PBAC response (\$ [REDACTED] per patient per course; \$ [REDACTED] effective price per vial); and the March 2019 submission (\$ [REDACTED] per patient per course; \$ [REDACTED] effective price per vial) due to the increased rebates proposed.

4.16 The table below shows the impact of the different rebates proposed across the submissions, and the different assumptions regarding the percent reduction in use in the R/R setting (discussed in Paragraphs 4.24 - 4.25 below), on the financial estimates. As shown in the table below, utilisation of inotuzumab ozogamicin (herein referred to as inotuzumab) in the R/R setting would also be affected by listing of blinatumomab in the MRD setting.

Table 3: Estimated financial implications in the current and previous submissions

	July 2019 resubmission	March 2019 pre-PBAC response	March 2019 submission
Proposed rebate			
In MRD setting	█%	█%	█%
In R/R setting	█%	█%	█%
Cost per patient per course			
In MRD setting (avg. 53 vials)	\$ █	\$ █	\$ █
In R/R setting (avg 42 vials) ^a	\$ █	\$ █	\$ █
ICER/QALY in MRD setting	\$ █	\$ █	\$ █
% reduction in R/R setting	█% Pre-PBAC response: █%	█%	-
Cost to PBS/RPBS over 6 years using the proposed rebates and % reduction in R/R use (all other assumptions per the July 2019 resubmission)			
In MRD setting (no offsets) ^b	\$ █ million	\$ █ million	\$ █ million
Total cost of blinatumomab and inotuzumab in R/R setting ^c	\$ █ million Pre-PBAC response: \$ █ million	\$ █ million	-
Total cost of blinatumomab and inotuzumab in MRD and R/R	\$ █ million Pre-PBAC response: \$ █ million	\$ █ million █% rebate in both settings, █% reduction in use in R/R setting) \$ █ million with only the rebates changed (i.e. █% rebate in both settings, █% reduction in R/R setting)	-

^a Calculated using the same assumptions as were used in the financial estimates for MRD (except for the average number of vials per patient), for example private setting (41%) and public hospital use (59%); starting in 2020 etc.

^b Blinatumomab drug costs only, no offsets included (i.e. no offsets for reduced consolidation chemotherapy, and no offsets for reduced use of blinatumomab or inotuzumab in the R/R setting). Based on Row 89 of 'Financial implications' worksheet of 'BlinMD_Section4model_Apr19 update.xlsx' with proposed rebated updated in Cell C44 of 'inputs' worksheet.

^c To facilitate the comparison, only the proposed rebate and percent reduction in R/R use were changed in the current minor resubmission's worksheets (e.g. Ph+ patients and inotuzumab were assumed to be subsidised in the R/R setting).

Note: There was a discrepancy in the way the effective price of blinatumomab was calculated between the various worksheets presented with the minor resubmission. This has not been corrected in the figures presented in the Minutes.

The redacted table shows ICERs in the range of \$45,000/QALY - \$105,000/QALY, and the total estimated cost to PBS over 6 years was in the range of \$15,000/QALY - \$45,000/QALY to \$45,000/QALY - \$105,000/QALY.

4.17 The current resubmission proposed an increased rebate (█%) in the MRD setting only, which resulted in an ICER less than \$45,000/QALY - \$75,000/QALY in the MRD setting. The March 2019 pre-PBAC response had proposed a █% rebate across both the MRD and R/R settings. However, as shown in the table above the total financial impact of either set of proposed rebates was similar, with the estimated total cost over six years of blinatumomab and inotuzumab in both settings being more than \$100 million with a █% rebate in both settings (per the March 2019 pre-PBAC response), versus \$60 - \$100 million with rebates of █% and █% in the MRD and R/R settings, respectively (per the current minor resubmission).

Estimated PBS usage & financial implications

Relevant excerpts from March 2019 blinatumomab PBAC Minutes:

4.18 In March 2019, the PBAC considered that even with a lower ICER, “the magnitude and durability of the overall survival benefit included in the model was highly uncertain, and it was unclear whether blinatumomab when used earlier in the treatment pathway would reduce long-term relapse rates and also therefore the use of subsequent therapies in the R/R setting. Thus, the PBAC considered that it could only be satisfied that blinatumomab was sufficiently cost-effective if financial arrangements were put in place to ensure that savings due to reduced use of blinatumomab in the R/R setting would be realised” (March 2019 blinatumomab PBAC Minutes, paragraph 7.16).

Blinatumomab utilisation in the MRD setting

4.19 The only change to the financial estimates for blinatumomab in the MRD setting (without offsets for reduced use in the R/R setting), was that the resubmission updated the price of blinatumomab to reflect the proposed rebate of ██████% (and updated the estimates for an additional year of forward estimates). The estimates are shown in Table 4 below. The table also includes the resubmission’s estimates of cost offsets from reduced use of consolidation chemotherapy (the comparator), which was also unchanged from the previous submission).

Table 4: Estimated use and financial implications for blinatumomab in MRD setting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated (95% uptake)	█	█	█	█	█	█
'Adult equivalents' ^a	█	█	█	█	█	█
Total number of vials (53 vials)	█	█	█	█	█	█
Estimated financial implications of blinatumomab in the MRD setting (without offsets)						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Co-payments (\$23.51)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to PBS/RPBS less co-pay	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Previous submission Cost to PBS/RPBS less co-pay ^b	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Previous pre-PBAC response Cost to PBS/RPBS less co-pay ^b	\$ █	\$8 █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications (with offsets for reduced consolidation chemotherapy only)						
Cost to PBS/RPBS ^c	\$ -	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to PBS/RPBS (offsets for consolidation chemo only)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

^a Adult equivalents was calculated by the minor resubmission based on the assumption that paediatric patients receive 60% of the adult dose.

^b Year 1 was re-aligned to reflect the comparable time period (i.e. 2020). Cost to PBS/RPBS was based on the price proposed in the previous resubmission (█% rebate) and in the pre-PBAC response (█% rebate).

^c Offsets for reduced use of consolidation chemotherapy (hyper-CVAD): included offsets for imatinib in Ph+ patients (which may not be appropriate as patients may use blinatumomab in combination with TKIs); and inappropriately included PBS co-payments. A cost-saving of \$14,501 per patient was assumed based on the cost of hyper-CVAD per patient (\$17,606*80% compliance) less co-medications for blinatumomab (of \$34 per patient).

Source: 'BlinMRD_Section4model_Apr19 update.xlsx', Table 1 of minor resubmission

4.20 The estimated cost to the PBS/RPBS for blinatumomab in MRD (blinatumomab drug cost only, no offsets included) was less than \$10 million in Year 6 with a cumulative cost of \$30 - \$60 million over six years.

Reduced use of blinatumomab and inotuzumab in the R/R setting

4.21 The minor resubmission estimated the impact that listing blinatumomab for MRD would have on the use of blinatumomab and inotuzumab in the R/R setting. These estimates form the basis for the resubmission's proposed caps, and the resubmission proposed a █% rebate for expenditure above the caps for blinatumomab.

4.22 Key differences between the estimates presented in the minor resubmission and the March 2019 pre-PBAC response include that the minor resubmission:

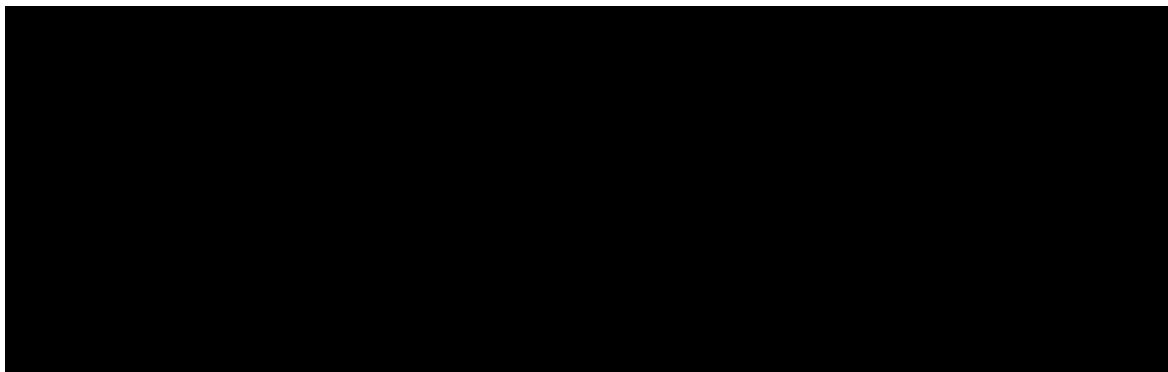
- Provided patient numbers to determine the impact on the R/R setting.
- Estimated the impact on inotuzumab, as inotuzumab was listed in the R/R setting on 1 May 2019 and patients can access blinatumomab and inotuzumab sequentially if required.
- Updated the estimates to reflect the extension of eligibility of blinatumomab and inotuzumab to include R/R patients whose condition is Philadelphia chromosome positive (as recommended at the May 2019 Intra-cycle PBAC meeting).

4.23 The minor resubmission estimated there would be a ■% reduction in the use of blinatumomab and inotuzumab in the R/R setting, which was based on the following key assumptions:

- ■% of patients respond to blinatumomab in the MRD setting. The resubmission stated this was based on Figure 2 of Gokbuget et al 2018.
- ■% of responding patients remain relapse-free due to use of blinatumomab in the MRD setting and thus no longer require blinatumomab (or inotuzumab) in the R/R setting. The resubmission stated that this was based on Figure 3 of Gokbuget et al 2018. It was unclear which specific data this was based on within Figure 3 of Gokbuget; however, the PBAC considered that an assumption that ■% of patients are relapse-free at two years broadly aligned with the comparative efficacy data provided in the previous submission.

4.24 Figure 2 outlines the method used in the resubmission to calculate the impact on utilisation in the R/R setting, and Table 5 shows the patient numbers each year. The resubmission's calculations also include the following assumptions which were previously accepted by the PBAC in the R/R setting: ■% uptake of the first 'biologic' (i.e. either blinatumomab or inotuzumab); and ■% of these patients use a second biologic.

Figure 2: Minor resubmission's estimates of the effect on blinatumomab and inotuzumab use in R/R setting (derivation of ■% reduction in use in the R/R setting, as estimated in minor resubmission)



Source: Compiled during preparation of the Minor Overview based on 'RR estimates and impact of MRD.xlsx'

Bold text indicates patients who are no longer eligible for blinatumomab or inotuzumab in the R/R setting, as a result of blinatumomab use in the MRD setting.

Patient numbers are based on 'adult equivalents' in Year 1 of MRD estimates.

Table 5: Estimated reduction in use of blinatumomab and inotuzumab in the R/R setting (per resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated financial implications of blinatumomab in the MRD setting (without offsets)						
Cost to PBS/RPBS less co-payments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Offsets for reduced use of blinatumomab or inotuzumab in the R/R setting						
'Adult equivalents' treated in the MRD setting	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Responders (78%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Responders 'cured' (50%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
No longer receive 1st biologic in R/R (80%) [A]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
No longer receive 2nd biologic in R/R (50%) [B]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non-responders (22%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- receive inotuzumab (1st biologic) in R/R (80%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- no longer receive blinatumomab (2 nd biologic) in R/R (50%) [C]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Fewer courses of blinatumomab or inotuzumab in R/R (A+B+C with lag)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

^a Lag times were applied in the minor resubmission

Source: Table 4, minor resubmission; 'RR estimates and impact of MRD.xlsx'; 'BlinMRD_Section4model_Apr19.xlsx'

The redacted table shows that at Year 6, the estimated costs to the PBS would be less than \$10 million.

4.25 The minor resubmission assumed:

- patients who respond and are relapse free at around two to three years of follow-up will remain relapse-free (upper row of Figure 2). The PBAC considered this was generally consistent with the previous submission’s claims that blinatumomab is associated with durable relapse-free survival and improved overall survival.
- patients who respond to blinatumomab in MRD but subsequently relapse will be eligible for potential sequential use of blinatumomab and inotuzumab in the R/R setting (middle row of Figure 2). The minor resubmission assumed that less than 10,000 patients (of the less than 10,000 treated in the MRD setting) would use three courses of biologics e.g. blinatumomab in the MRD setting, followed by inotuzumab in the R/R setting, followed by blinatumomab in a subsequent relapse (may underestimate the reduced use in the R/R setting). The Minor Overview considered this may underestimate the reduced use in the R/R setting.
- “non-responders” to blinatumomab at MRD would only be eligible for inotuzumab (lower row of Figure 2). The estimates assumed that [REDACTED] non-responders would be eligible for inotuzumab with an [REDACTED]% uptake applied. The Minor Overview considered this may not be reasonable as uptake may be lower in MRD non-responders (may underestimate the reduced use in the R/R setting).

4.26 The resubmission also assumed there would be a one year lag between when a patient receives blinatumomab in the MRD setting and when offsets for reduced use of blinatumomab or inotuzumab in the R/R setting would occur.

- 4.27 The Minor Overview noted that the assumptions applied in the resubmission would have resulted in a [REDACTED]% reduction in the estimated utilisation and expenditure on blinatumomab and inotuzumab in the R/R setting in Years 2 to 6 (calculation shown in Table 6). The Minor Overview noted that the previous submission’s pre-PBAC response had estimated a [REDACTED]% reduction in blinatumomab use in the R/R setting (March 2019 blinatumomab PBAC Minutes, paragraph 7.17), which would have resulted in lower overall expenditure caps.
- 4.28 The pre-PBAC response noted that the Minor Overview had suggested that a [REDACTED]% reduction in R/R use may be an underestimate and stated the Sponsor was “willing to agree overall caps for blinatumomab that represent a [REDACTED]% reduction in use of blinatumomab in the R/R setting with maximum uptake in the MRD setting” (see Table 7).
- 4.29 The table below shows the estimated reduction in expenditure in the R/R setting, as estimated in the resubmission and the pre-PBAC response.

Table 6: Estimated impact on expenditure on blinatumomab and inotuzumab in the R/R setting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Minor resubmission: Cost to PBS/RPBS of blinatumomab and inotuzumab in R/R setting						
without MRD listing ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS for reduced use of R/R blinatumomab + inotuzumab ^b	\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
with MRD listing	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
% reduction with MRD listing ^c	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Pre-PBAC response: Cost to PBS/RPBS of blinatumomab and inotuzumab in R/R setting						
% reduction with MRD listing	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Cost to PBS/RPBS for reduced use of R/R blinatumomab+inotuzumab	\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
with MRD listing	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Based on figures provided by the sponsor ('RR estimates and impact of MRD.xlsx', 'Pt numbers & cost' worksheet, Row 78).

^b Based on Row 78 of 'Pt numbers & cost' worksheet of 'RR estimates and impact of MRD.xlsx' minus Row 28 of 'MRD impact Ph- & Ph+' worksheet.

^c Calculated by the Minor Overview as the difference between expenditure on blinatumomab and inotuzumab in the R/R setting with and without the MRD listing. This was calculated to compare the estimates provided in the minor resubmission with those provided in the March 2019 pre-PBAC response.

Source: Table 4, minor resubmission; 'RR estimates and impact of MRD.xlsx'; 'BlinMRD_Section4model_Apr19.xlsx'

- 4.30 With the [REDACTED]% reduction in use of blinatumomab and inotuzumab in the R/R setting, as proposed in the pre-PBAC response, the reduction in PBS/RPBS expenditure in the R/R setting is estimated to be less than \$10 million in Year 6 and \$20 - \$30 million over six years.
- 4.31 The table below shows the total net impact of listing blinatumomab in the MRD setting (i.e. with the aforementioned cost offset plus the offset for reduced use of consolidation chemotherapy in the MRD setting).

Table 7: Estimated net cost to the PBS/RPBS of listing blinatumomab in MRD setting (with all drug offsets)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Minor resubmission						
Cost to PBS/RPBS of blinatumomab (no offsets)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS of consolidation chemotherapy	-\$1,036,986	-\$1,060,797	-\$1,084,607	-\$1,108,418	-\$1,132,229	-\$1,156,039
Cost to PBS/RPBS for reduced use of R/R blinatumomab and inotuzumab	\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Net cost to the PBS/RPBS of listing blinatumomab for MRD	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Pre-PBAC response (only difference is % reduction in R/R use, so first two rows are unchanged)						
Cost to PBS/RPBS for reduced use of R/R blinatumomab and inotuzumab	\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to the PBS/RPBS of listing blinatumomab for MRD	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Tables 3 and 4 above, 'RR estimates and impact of MRD.xlsx'; 'BlinMRD_Section4model_Apr19.xlsx'

4.32 The overall net cost to the PBS/RPBS of listing blinatumomab in the MRD setting (with all PBS/RPBS offsets) would be less than \$10 million in Year 6 and \$20 - \$30 million over 6 years (using the assumptions outlined in the pre-PBAC response).

Financial Management – Risk Sharing Arrangements

4.33 The overall caps for blinatumomab proposed in the resubmission and pre-PBAC response are presented in the table below.

4.34 The proposed caps stated in the resubmission did not include inotuzumab and thus the resubmission estimated that the relative market share of each agent in the R/R setting would be [REDACTED]% blinatumomab and [REDACTED]% inotuzumab. The minor resubmission stated “blinatumomab will be used more than inotuzumab in the R/R setting because it will be the preferred treatment for transplant-eligible patients and for patients who responded to blinatumomab in the MRD setting”. The minor resubmission further stated that with sequential use permitted, the maximum share blinatumomab could have in the R/R setting would be [REDACTED]%, and that a share of [REDACTED]% was assumed to account for non-responders in MRD who will not be able to access blinatumomab in the R/R setting.

Table 8: Resubmission’s proposed overall caps for blinatumomab in MRD and R/R (excludes inotuzumab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost to PBS/RPBS of blinatumomab in R/R setting (60% market share)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS of blinatumomab in MRD	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Minor resubmission: Total cost of blinatumomab = caps (31% reduction in R/R setting in Years 2 to 6)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Pre-PBAC response: Total cost of blinatumomab = caps (40% reduction in R/R setting in Years 2 to 6)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 2 of minor resubmission, Table 1 of pre-PBAC response

- 4.35 In March 2019, the PBAC “considered that if a single RSA subsidy cap was to be enacted any increase in subsidy caps over that of the current R/R setting would need to account for both the increase in eligible patients due to MRD and the expected decrease in patients in the R/R setting” (March 2019 blinatumomab PBAC Minutes, paragraph 7.19).
- 4.36 The minor resubmission stated that the sponsor’s “strong preference is for one set of overall caps for blinatumomab”. The pre-PBAC response stated “it would not be reasonable to simply reduce the existing R/R caps by [REDACTED]% from the outset and establish a separate RSA for blinatumomab in the MRD setting as there is a high degree of uncertainty in both the magnitude and speed of uptake of blinatumomab in MRD” and that “Instead, Amgen has proposed overall caps for blinatumomab that allow for the uncertain uptake in MRD and address the PBAC’s request that the caps should reflect a reduction in R/R use.”
- 4.37 The table above does not include the cost of inotuzumab. The minor resubmission estimated there would also be a corresponding reduction in utilisation and expenditure on inotuzumab in the R/R setting (if blinatumomab were listed in the MRD setting). Using the minor resubmission’s estimates, the total impact on cap/s for both drugs is outlined below (for both MRD and R/R). A revised cap including inotuzumab is outlined in the table below.

Table 9: Cost to PBS/RPBS of both blinatumomab and inotuzumab in R/R setting if blinatumomab is listed in MRD (derived from the resubmission and pre-PBAC response's estimates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Minor resubmission						
Cost to PBS/RPBS of blinatumomab in both settings	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS of inotuzumab in R/R (40% market share)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost to PBS/RPBS of both drugs in both settings	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Pre-PBAC response						
Cost to PBS/RPBS of blinatumomab in both settings	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS of inotuzumab in R/R (40% market share)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost to PBS/RPBS of both drugs in both settings	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4 of minor resubmission (last row subtracted from second-last row)

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the Section 100 Authority Required (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) in haematological complete remission with minimal residual disease (MRD) following induction chemotherapy. The PBAC was satisfied that with the rebate proposed in the resubmission and a Risk Sharing Arrangement (RSA) with caps based on an estimated [REDACTED]% reduction in blinatumomab and inotuzumab use in the relapsed/refractory setting to manage the uncertainty in the financial impact of listing, blinatumomab would be sufficiently cost-effective in the MRD treatment setting.
- 5.2 The PBAC reiterated that in suitable patients, blinatumomab would be used as a bridge to transplant to improve the risk state of MRD positive patients prior to haematopoietic stem cell transplant (HSCT) as MRD positive disease is associated with a high risk of relapse. The PBAC reiterated that use of blinatumomab in the MRD setting would prevent or delay a proportion of use in the relapsed/refractory setting.
- 5.3 The PBAC recalled it previously considered that while blinatumomab is effective in eliminating MRD and is associated with durable relapse-free survival, it remained unclear whether blinatumomab would lead to long-term gains in overall survival given the lack of a reliable comparative data and the relative immaturity of the data from the BLAST study. However, the PBAC considered the updated data from the BLAST study (see paragraph 4.5) reinforced that treatment with blinatumomab may be associated with an overall survival advantage noting that the plateau in overall survival after 48 months indicated in the overall survival data available at the March 2019 consideration was maintained.

- 5.4 The PBAC maintained its previous consideration that blinatumomab and standard of care chemotherapy have different safety profiles, where both are associated with potentially life-threatening complications.
- 5.5 The PBAC noted that the ICER reduced from \$75,000-\$105,000/QALY in the March 2019 submission to \$45,000-\$75,000/QALY with the ██████% rebated proposed in the resubmission. This was consistent with the PBAC's previous advice where it considered that an ICER less than \$45,000-\$75,000/QALY would be required to account for uncertainties with the clinical data and economic model.
- 5.6 The PBAC noted that the estimated net cost to the PBS over six years (without including cost offsets) reduced from \$30-\$60 million in the March 2019 pre-PBAC response to \$30 - \$60 million with the proposed rebate of ██████%. The PBAC noted that while the pre-PBAC response to the March 2019 submission estimated a ██████% reduction in blinatumomab use in the relapsed/refractory setting if blinatumomab was listed in the MRD setting, key assumptions used by the resubmission to estimate the reduction in blinatumomab and inotuzumab use in the relapsed/refractory setting resulted in an estimated ██████% reduction. The PBAC considered that most of the assumptions used (see paragraphs 4.23 and 4.25) were reasonable however, considered that the proportion of patients that would utilise a third biologic was likely overestimated. The PBAC considered it was unlikely that all patients responsive to blinatumomab in the MRD setting who subsequently relapse will use both blinatumomab and inotuzumab in the relapsed/refractory setting or that all non-responders to blinatumomab in the MRD setting would be eligible for inotuzumab (e.g. not all B-ALL patients would be CD22 positive). As such, the PBAC considered that the estimated ██████% reduction in use of blinatumomab and inotuzumab in the relapsed/refractory setting may be an underestimate. The PBAC noted the proposal in the pre-PBAC response for overall caps for blinatumomab (i.e. caps which account for both blinatumomab utilisation in the MRD and relapsed/refractory setting) to include a ██████% reduction in use of blinatumomab in the relapsed/refractory setting and considered this would appropriate to manage the remaining uncertainty in the overall financial impact of listing. The PBAC considered this same proportion reduction (i.e. ██████%) in use of blinatumomab in the relapsed/refractory setting should also apply to inotuzumab.
- 5.7 The PBAC considered that if blinatumomab was listed for use in the MRD setting, uptake would likely be rapid and high and considered that the uptake rate of ██████%, as estimated in the resubmission, was appropriate.
- 5.8 The PBAC recalled its previous consideration that a Risk Sharing Arrangement (RSA) with a ██████% rebate on expenditure above the subsidy caps was appropriate given the uncertain effect on blinatumomab use in the relapsed/refractory setting, the uncertain patient population and the likely underestimated number of vials per patient.

- 5.9 The PBAC noted that the resubmission indicated the sponsor's preference for a single set of caps for blinatumomab to encompass use in both the MRD and relapsed/refractory setting. The PBAC considered that if a single RSA subsidy cap was to be enacted, the cost of both blinatumomab and inotuzumab and a 40% decrease in use in the relapsed/refractory setting would need to be accounted for when calculating a total cap for both medicines across both settings. On this basis, the PBAC considered that an alternative arrangement which would have the same effect of maintaining overall caps for blinatumomab across both populations would also be appropriate.
- 5.10 The PBAC considered that the proposed criteria specifying "treatment must be the sole PBS-subsidised therapy for this condition" should be removed to allow use in combination with a TKI in Ph+ patients. This would align with the PBAC's previous advice that the restriction should allow concomitant use of blinatumomab and a TKI.
- 5.11 The PBAC considered that next generation sequencing technology should not be included in the restriction as a method to measure MRD until further evidence on the reliability of this methodology to detect MRD becomes available.
- 5.12 The PBAC found that the three criteria prescribed by *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for blinatumomab:
- a. Treatment with blinatumomab is expected to provide a substantial and clinically relevant improvement in efficacy over alternate therapies on the basis of eliminating MRD.
 - b. Treatment with blinatumomab is not expected to address a high and urgent unmet clinical need because other subsidised therapies are available.
 - c. It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.13 The PBAC advised that under subsection 101 (3BA) of the *National Health Act 1953*, that blinatumomab should not be treated as interchangeable on an individual patient basis with any other drugs. The PBAC noted that no other drugs were currently listed for the treatment of MRD.
- 5.14 The PBAC advised that blinatumomab is not suitable for prescribing by nurse practitioners as chemotherapy agents are currently considered to be out of scope for prescribing by nurse practitioners.
- 5.15 The PBAC recommended that the Early Supply Rule should not apply.
- 5.16 The PBAC noted that this submission was not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Proprietary Name and Manufacturer	
BLINATUMOMAB 38.5 µg, injection, 1 vial	784 µg	1	Blincyto®	Amgen Australia Pty Ltd

Category / Program	Section 100 – Efficient funding of Chemotherapy (S100 EFC Public) Section 100 – Efficient funding of Chemotherapy (S100 EFC Private)
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
Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	Minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (B-ALL) in patients with complete haematological remission
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	The condition must be B-cell precursor acute lymphoblastic leukaemia with an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, AND The condition must not be present in the central nervous system or testis, AND Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy, AND Patient must have achieved a complete remission, AND Patient must have minimal residual disease defined as at least 10 ⁻⁴ (0.01%) blasts based on measurement in bone marrow, documented after an interval of at least 2 weeks from last systemic chemotherapy,

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	<p>AND</p> <p>Minimal residual disease must be measured using polymerase chain reaction or flow cytometry,</p> <p>AND</p> <p>The treatment must not be more than two treatment cycles under this restriction in a lifetime.</p>
<p>Prescriber Instructions</p>	<p>According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.</p> <p>For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.</p> <p>An amount of 784 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.</p> <p>Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) a completed authority prescription form; (2) a completed Minimal residual disease positive Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and (3) proof of complete remission; (4) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy; and (5) a copy of the most recent MRD results and bone marrow biopsy report of no more than one month old at the time of application. <p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time when an assessment is required must cease PBS-subsidised therapy with this agent.</p>
<p>Administrative Advice</p>	<p>A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p>

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	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Caution	Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.

Treatment phase:	Continuing treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	<p>Patient must have previously received PBS-subsidised initial treatment with this drug for this condition,</p> <p>AND</p> <p>Patient must have achieved a complete remission,</p> <p>AND</p> <p>Patient must be MRD negative defined as either undetectable using the same assay as used to determine original eligibility or less than 10^{-4} (0.01%) blasts based on measurement in bone marrow,</p> <p>AND</p> <p>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>The treatment must not be more than two treatment cycles under this restriction in a lifetime.</p>
Prescriber instructions:	<p>For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.</p> <p>An amount of 784 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.</p> <p>Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.</p> <p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent</p>

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	at the time when an assessment is required must cease PBS-subsidised therapy with this agent.
Administrative Advice:	<p>A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.</p> <p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time when an assessment is required must cease PBS-subsidised therapy with this agent.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Special Pricing Arrangements apply.</p>
Cautions:	Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.

6.2 Amend existing listings as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
BLINATUMOMAB 38.5 µg, injection, 1 vial	651 µg	0	Blincyto®	Amgen Australia Pty Ltd

Category / Program:	Section 100 – Efficient funding of Chemotherapy (S100 EFC Public) Section 100 – Efficient funding of Chemotherapy (S100 EFC Private)
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
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required – In Writing
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase	Induction treatment
Clinical criteria	<p>The condition must be relapsed or refractory B-precursor cell ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less,</p> <p>AND</p> <p>The condition must not be present in the central nervous system or testis,</p> <p>AND</p> <p>Patient must have previously received a tyrosine kinase inhibitor if the condition is Philadelphia chromosome positive,</p>

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	<p>AND</p> <p>Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy,</p> <p>AND</p> <p>Patient must not have received more than 1 line of salvage therapy,</p> <p>AND</p> <p><i>Patient must not have received blinatumomab previously for the treatment of minimal residual disease</i></p> <p>OR</p> <p><i>Patient must have had a relapse-free period of at least six months following completion of treatment with blinatumomab for minimal residual disease,</i></p> <p>AND</p> <p>The condition must have more than 5% blasts in bone marrow,</p> <p>AND</p> <p>The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.</p>
<p>Prescriber Instructions:</p>	<p>According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a health care professional or hospitalisation is recommended.</p> <p>An amount of 651 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 1. An amount of 784 microgram, which may be obtained under Induction treatment - balance of supply restriction, will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 2.</p> <p>Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form;</p> <p>(2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form;</p> <p>(3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage;</p> <p><i>(4) If applicable, the date of completion of blinatumomab treatment for minimal residual disease and the date of the patient's subsequent relapse; and</i></p> <p>(5) a copy of the most recent bone marrow biopsy report of no more than one month old at the time of application.</p>
<p>Administrative Advice:</p>	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p>

	<p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
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Item codes 11116C and 11118E

7 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.

8 Sponsor's Comment

Amgen is pleased that blinatumomab will soon be available on the PBS for the treatment of minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (B-ALL) in patients with complete haematological remission.