

5.07 INOTUZUMAB OZOGAMICIN, Powder for IV infusion, 1 mg vial, Besponsa[®], Pfizer Australia

1 Purpose of Application

1.1 The submission requested a Section 100 Authority Required (In Writing) Efficient Funding of Chemotherapy listing for inotuzumab ozogamicin (herein referred to as 'inotuzumab') for the treatment of relapsed or refractory Philadelphia chromosome negative CD22 positive B-cell precursor acute lymphoblastic leukaemia (B-ALL). This was the first consideration of inotuzumab by the PBAC.

1.2 Listing was requested on a cost-minimisation basis compared to blinatumomab.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults with relapsed/refractory Philadelphia chromosome negative, CD22-positive, B-cell precursor acute lymphoblastic leukaemia.
Intervention	Inotuzumab by intravenous infusion over 3-4 week cycles. 1.8 mg/m ² per cycle (0.8 mg/m ² on Day 1, 0.5 mg/m ² on Days 8 & 15). First cycle over 21 days and subsequent cycles of 28 days with a treatment free interval from day 16 to 28. Maximum of 6 cycles.
Comparator	Blinatumomab by continuous intravenous infusion over 28 day cycles, followed by a 14 day treatment free interval. Dose of 9 mcg/m ² /day for the first 7 days of Cycle 1, then 28 mcg/m ² /day for remainder of Cycle 1 and all subsequent cycles. Maximum of 5 cycles.
Outcomes	Complete remission, complete remission with incomplete haematological recovery, overall survival, MRD negativity, progression free survival, haematopoietic stem cell transplant rate, duration of response, EQ-5D, EORTC QLQ-C30, safety outcomes (adverse events, treatment discontinuation/interruption).
Clinical claim	In the treatment of relapsed/refractory, Philadelphia chromosome negative, CD22-positive, B-cell precursor acute lymphoblastic leukaemia, inotuzumab is non-inferior in terms of efficacy and different, but non-inferior in terms of safety compared to blinatumomab.

Source: Table 1.1.1, p.14 of the submission.

Abbreviations: EQ-5D, EuroQoL-5 Dimension Questionnaire; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; MRD, minimal residual disease.

2 Requested listing

2.1 The requested PBS listing is outlined below, with the PBAC's suggested additions in italics and deletions in strikethrough.

Induction

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
INOTUZUMAB OZOGAMICIN				
1 mg vial powder for injection	4 3384 mcg	2	\$ [REDACTED] (Public hospital) \$ [REDACTED] (Private hospital)	Besponsa [®] Pfizer Australia P/L

Public Summary Document – November 2018 PBAC Meeting

Category/Program:	S100 – Efficient Funding of Chemotherapy (EFC)
PBS indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	Initial <i>Induction treatment</i>
Restriction:	Authority Required - In Writing
Treatment criteria:	Inotuzumab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
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 AND The condition must not be present in the central nervous system or testis, AND The patient <i>Patient</i> must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy, AND <i>Patient must not have received more than 1 line of salvage therapy</i> AND The condition must be Philadelphia chromosome negative, AND The condition must be CD22-positive, AND The condition must have more than 5% blasts in bone marrow, AND The treatment must not be more than 3 treatment cycles under this restriction in a lifetime.</p>
Population criteria:	The patient must be 18 years or over.
Prescriber instructions:	<p>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</p> <p><i>The authority application must be made in writing and must include:</i></p> <ol style="list-style-type: none"> <i>(1) a completed authority prescription form;</i> <i>(2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and</i> <i>(3) a signed patient acknowledgement; and</i> <i>(4) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage; and</i> <i>(5) a copy of the most recent bone marrow biopsy report of no more than one month old at the time of application.</i> <p><i>The treatment must not exceed 0.8mg per m² for the first dose of a treatment cycle (Day 1), and 0.5mg per m² for subsequent doses (Days 8 and 15) within a treatment cycle.</i></p>

Public Summary Document – November 2018 PBAC Meeting

Administrative advice	<p>Once a patient achieves complete remission or complete remission with partial haematological recovery, a new prescription must be written under the consolidation treatment phase.</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>A complete remission with partial haematological recovery is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a partial recovery of peripheral blood counts with platelets of greater than 50,000 per microliter, and absolute neutrophil count (ANC) of greater than 500 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>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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>
Cautions:	<p>Careful monitoring of patients is required due to risk of developing hepatotoxicity, including life-threatening hepatic veno-occlusive disease, and the increased risk of post-haematopoietic stem cell transplant non-relapse mortality observed in patients treated with inotuzumab.</p>

Continuing

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
INOTUZUMAB OZOGAMICIN 1 mg vial powder for injection	3 2820 mcg	4	\$ [REDACTED] (Public hospital) \$ [REDACTED] (Private hospital)	Besponsa® Pfizer Australia P/L
Category/Program:	S100 – Efficient Funding of Chemotherapy (EFC)			
PBS indication:	Acute lymphoblastic leukaemia (ALL)			
Treatment phase:	Consolidation treatment			
Restriction:	Authority Required - In Writing Telephone			
Treatment criteria:	Inotuzumab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.			

Public Summary Document – November 2018 PBAC Meeting

Clinical criteria:	<p>Patient must have previously received PBS-subsidised <i>induction</i> treatment with this drug for this condition, AND Patient must have achieved a complete remission (CR) or complete remission; OR Patient must have achieved a complete remission with partial haematological recovery (CRi), AND The treatment must not be more than 5 treatment cycles under this restriction in a lifetime, AND <i>Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug</i></p>
Prescriber instruction:	<p>Treatment with inotuzumab-ozogamicin for ALL this drug for this condition must not exceed 6 treatment cycles in a lifetime.</p> <p>Patients who fail to demonstrate a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) after 3 cycles of PBS-subsidised treatment with this agent must cease PBS-subsidised treatment with this agent.</p>
Administrative advice:	<p><i>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.</i></p> <p><i>A complete remission with partial haematological recovery is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a partial recovery of peripheral blood counts with platelets of greater than 50,000 per microliter, and absolute neutrophil count (ANC) of greater than 500 per microliter.</i></p> <p><i>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.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>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).</i> <i>Special Pricing Arrangements apply.</i></p>
Cautions:	<p><i>Careful monitoring of patients is required due to risk of developing hepatotoxicity, including life-threatening hepatic veno-occlusive disease, and the increased risk of post-haematopoietic stem cell transplant non-relapse mortality observed in patients treated with inotuzumab.</i></p>

Grandfathering

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
INOTUZUMAB OZOGAMICIN 1 mg vial powder for injection	3384 mcg	1	\$ [REDACTED] (Public hospital) \$ [REDACTED] (Private hospital)	Besponsa® Pfizer Australia P/L

Category/Program:	S100 – Efficient Funding of Chemotherapy (EFC)
PBS indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	Induction treatment Grandfathering treatment
Restriction:	S100 – Efficient Funding of Chemotherapy (EFC) <input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Inotuzumab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
Clinical criteria:	<p>The condition must be relapsed or refractory B-precursor cell ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2 or less,</p> <p>AND</p> <p>The patient must have a documented history of receiving 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 2 lines of salvage therapy</p> <p>AND</p> <p>The condition must be Philadelphia chromosome negative,</p> <p>AND</p> <p>The condition must be CD22 positive,</p> <p>AND</p> <p>The condition Patient must have a documented history of more than 5% blasts in bone marrow prior to when the patient commenced inotuzumab,</p> <p>AND</p> <p>The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.</p> <p>AND</p> <p>The patient must have received treatment with this drug for this condition prior to [DATE OF PBS-LISTING],</p> <p>AND</p> <p>Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.</p>
Population criteria	The patient must be 18 years or over.
Prescriber Instructions:	<p>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p> <p>Treatment with inotuzumab for ALL this drug for this condition must not exceed 6 treatment cycles in a lifetime.</p> <p>Patients who have received up to three treatment cycles as induction therapy with this drug for this condition prior to [DATE OF PBS LISTING] must have achieved a complete remission, or a complete remission with partial haematological recovery in order to continue with PBS-subsidised treatment with this drug.</p>

Public Summary Document – November 2018 PBAC Meeting

	<p>Patients who have received at least one treatment cycle as consolidation therapy with this drug for this condition prior to [DATE OF PBS LISTING] must have achieved a complete remission, or a complete remission with partial haematological recovery in order to continue with PBS-subsidised treatment with this drug.</p> <p>Patients who fail to demonstrate a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) after 3 cycles of PBS-subsidised treatment with this agent must cease PBS-subsidised treatment with this agent.</p> <p><i>The authority application must be made in writing and must include:</i></p> <ol style="list-style-type: none"> (1) a completed authority prescription form; (2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and (3) evidence that the condition is CD22-positive; and (4) date of most recent inotuzumab ozogamicin dose, if this was for induction or consolidation therapy, and how many treatment cycle(s) of PBS-subsidised inotuzumab ozogamicin will be required for completion of induction or consolidation therapy; and (5) date of latest chemotherapy prior to receiving non-PBS subsidised inotuzumab ozogamicin, and if it was the initial chemotherapy regimen or for salvage therapy and what line of salvage; and (6) a copy of bone marrow biopsy report prior to receiving non-PBS subsidised inotuzumab ozogamicin.
Definitions	<p>A complete remissionCR is defined as bone marrow blasts of less than or equal to 5%, <5% blasts in the bone marrow 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. and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets $\geq 100 \times 10^9/L$ and absolute neutrophil counts [ANC] $\geq 1 \times 10^9/L$) and resolution of any extramedullary disease.</p> <p>A complete remission with partial haematological recovery is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a partial recovery of peripheral blood counts with platelets of greater than 50,000 per microliter, and absolute neutrophil count (ANC) of greater than 500 per microliter. CRi is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, incomplete recovery of peripheral blood counts (platelets $< 100 \times 10^9/L$ and/or ANC $< 1 \times 10^9/L$) and resolution of any extramedullary disease.</p>
Administrative Advice:	<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). 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 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. No increase in the maximum number of repeats may be authorised.</p> <p>An increase in the maximum number of repeats of up to 2 will be allowed for completion of induction therapy.</p> <p>An increase in the maximum number of repeats of up to 4 will be allowed for completion of consolidation therapy.</p> <p>Special Pricing Arrangements apply.</p>

Cautions:	<p>Careful monitoring of patients is required due to risk of developing hepatotoxicity, including life-threatening hepatic veno-occlusive disease, and the increased risk of post-haematopoietic stem cell transplant non-relapse mortality observed in patients treated with inotuzumab.</p> <p>Careful monitoring of patients is required due to risk of developing veno-occlusive disorder (VOD) / sinusoidal obstructive syndrome (SOS).</p>
-----------	--

- 2.2 The submission acknowledged that a special pricing arrangement applies to blinatumomab, and requested that a similar special pricing arrangement be applied to inotuzumab.
- 2.3 The requested restriction limited the number of treatment cycles to a maximum of three cycles of initial therapy and five cycles of consolidation therapy, but with a maximum of six cycles in a lifetime. This was because some patients may only require one cycle in the initial setting before achieving a CR or CRi and moving onto the consolidation dosing regimen. The proposed maximum number of cycles in each setting was appropriate given the differences in dosing between the induction and consolidation settings. To clarify the intent, administrative advice has been included in the initial restriction to outline that once a patient achieves CR or CRi, a new prescription must be written under the consolidation treatment phase.
- 2.4 The PBAC considered that the inotuzumab restriction should be consistent with the existing blinatumomab restriction where possible. In particular, the PBAC considered the two restrictions should be consistent or parallel regarding:
- Age criteria. The blinatumomab listing does not specify an age criterion while the requested inotuzumab restriction limited use to patients aged 18 years and over. This difference was based on: the TGA-registered indication for inotuzumab, which states that it is for the treatment of adults; and the INO-VATE ALL trial of inotuzumab, which was conducted in patients aged 18 years and over. However, the PBAC considered that there may be a clinical role for inotuzumab in patients aged less than 18 years and considered that the restriction should not specify an age criteria.
 - The definitions of CR or CRi in the proposed inotuzumab restriction should be amended to align with those included in the blinatumomab restriction.
 - The blinatumomab restriction cautions that careful monitoring of patients is required due to the risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) infection. The PBAC considered that a parallel caution is required in the inotuzumab restriction regarding the risk of hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease (VOD), and the increased risk of post-HSCT non-relapse mortality, for which there are black box warnings in the inotuzumab Product Information.
 - The PBAC considered that a note explaining the recommended dosing of inotuzumab should be included in the Prescriber Instructions in the initial setting.

The recommended dose of inotuzumab is 0.5 mg/m² per dose, except a higher dose (0.8 mg/m²) is recommended on Day 1 of Cycle 1, and also on Day 1 of Cycles 2 and 3 if CR or CRi is not achieved.

- Each drug should only be permitted to be used for one course per lifetime.
- 2.5 The requested restriction for initiation of inotuzumab requires patients to have an ECOG status of ≤ 2 , consistent with the inclusion criteria of the INO-VATE ALL and TOWER trials. However, the current blinatumomab listing requires an ECOG status of < 2 (i.e. it does not include patients with an ECOG status of 2), reflecting a narrower population with less severe/progressed disease. The PSCR re-iterated that listing was requested for patients with ECOG status of ≤ 2 , stating that 13% to 15% of patients in the key trials had an ECOG status of 2. The ESC considered that assessment of ECOG status could be subjective and, in clinical practice, this criterion was unlikely to restrict use. The PBAC considered that it would be appropriate to allow inotuzumab and blinatumomab to be used in patients with ECOG status of ≤ 2 , and noted that this would require an amendment to extend the existing restriction for blinatumomab.
- 2.6 The PBAC considered that the inotuzumab restriction should only allow use in first or second salvage, consistent with the inclusion criteria in the INO-VATE ALL trial. The PBAC noted that blinatumomab is currently subsidised for use in any line of salvage. While the PBAC noted that patients in third or later salvage were included in the TOWER trial of blinatumomab, it recalled that pre-specified subgroup analyses had indicated that blinatumomab was associated with an uncertain impact on overall survival when used in the third or later salvage settings (Kantarjian 2017)¹. Thus, the PBAC considered that the PBS restriction for blinatumomab should be updated to allow use only in first and second salvage, consistent with the restriction recommended for inotuzumab, and in line with the population for whom the clinical evidence suggests there is likely to be the most benefit. The PBAC considered this change was necessary because, with a second agent available, the number of patients proceeding to third or later salvage will increase over time.
- 2.7 The PBAC considered that the aspects of the inotuzumab restriction that were not appropriate to align with the blinatumomab restriction are:
- Proof of target expression: The inotuzumab restriction should limit treatment to patients with CD22 expression, consistent with the mechanism of action of inotuzumab and the inclusion criteria in the INO-VATE ALL trial. There is no such criterion in the blinatumomab restriction.
 - Exclusion of patients with CNS and testicular leukaemia: The blinatumomab restriction states that “the condition must not be present in the central nervous

¹ Kantarjian H, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* 2017; 376:836-847

system or testis”. The ESC noted that inotuzumab is not contraindicated in patients with CNS disease, while the Product Information for blinatumomab includes a special warning/precaution about neurological events. Thus, the ESC and the PBAC considered that a parallel criterion restricting use of inotuzumab in patients whose condition is present in the CNS or testis would not be required.

- Required hospitalisation: The blinatumomab listing notes that administration requires patient hospitalisation for nine days in the first cycle of treatment and two days in every subsequent cycle, while the inotuzumab does not specify any hospitalisation requirements consistent with the respective Product Information of the two drugs. While the ESC and PBAC advised that inotuzumab is often administered as an inpatient (at least initially) due to the nature of the disease and associated toxicities, the ESC and PBAC noted that the Product Information for inotuzumab does not specify a recommended hospitalisation period.
- 2.8 The requested restriction would allow patients who have been treated with inotuzumab to receive blinatumomab in a subsequent relapse, and vice versa.
- 2.9 The PSCR stated that the clinical management algorithm proposed in the submission did not include sequential use of inotuzumab and blinatumomab. The ESC noted that sequential use was not assessed in the clinical trials and thus the impact on incremental effectiveness was unknown. Notwithstanding this, the ESC considered that there may be a clinical place for sequential use of inotuzumab and blinatumomab in those patients who do not receive a HSCT or who do not achieve CR/CRi following a HSCT. The ESC considered that neither inotuzumab nor blinatumomab are likely to be curative as stand-alone treatment, and patients are likely to use these agents as a bridge to HSCT, CAR T-cell therapy or clinical trial therapy, or as sequential therapy to prolong life.
- 2.10 The PBAC noted that no data had been provided regarding the impact of sequential use on incremental efficacy. However, the PBAC considered that sequential use of blinatumomab and inotuzumab (in either order) was appropriate given their differing mechanisms of action, and the clinical need for additional therapeutic options for patients who are unable to have a HSCT or who progress after a HSCT, as such patients are likely to cycle through all available therapies. The PBAC considered that each agent should only be used once per lifetime.
- 2.11 The submission stated that a ‘small number’ of patients receiving compassionate access to treatment with inotuzumab at the time of PBS-listing will require grandfathering onto PBS-listed treatment. The financial estimates assumed that ■■■ grandfathered patients would require PBS-subsidised access to inotuzumab. The PSCR stated that patients who require grandfathering onto PBS treatment will otherwise meet the proposed PBS restriction.

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

3 Background

Registration status

- 3.1 Inotuzumab was listed on the Australian Register of Therapeutic Goods on May 17, 2018 for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL).

4 Population and disease

- 4.1 ALL is a rare malignant disease of the bone marrow (approximately 1-1.5/100,000 of the general population) in which lymphoid precursor cells proliferate. The incidence of ALL is highest in children under 5 years of age, declines slowly until the mid-20s and then begins to rise again slowly after 50 years of age. ALL may be related to either B-cell or T-cell precursors, with approximately 76% of adult and 85-90% of paediatric diagnoses identified as B-cell precursor ALL (B-ALL). B-ALL is also classified by Philadelphia chromosome expression (Ph+ or Ph-) or other cytogenetic and molecular subtype prognostic factors. CD22 is a B cell co-receptor that regulates B cell signalling, proliferation, adhesion, migration, and survival, and is expressed on the outer membrane of both normal and malignant B-cells from early progenitors to the mature B lymphocytes.
- 4.2 ALL is characterised by the emergence of haematological deficiencies, anaemia, thrombocytopenia and neutropenia that give rise to the distinctive symptoms of fatigue, bruising, bleeding, enlarged lymph nodes, fever, and infections. Hepatomegaly, splenomegaly, and lymphadenopathy may also be observed, as well as symptoms related to central nervous system or testicular involvement (headache, weakness, seizures, vomiting, testicular enlargement).
- 4.3 The key aim of treatment of adult patients with relapsed/refractory ALL is to achieve complete remission (CR) or complete remission with incomplete haematological recovery (CRi) to facilitate allogeneic haematopoietic stem cell transplant (HSCT), which may represent a cure in some patients. Patients with CR or CRi who are unable to undergo HSCT will receive maintenance therapy or “watch and wait”. Patients who do not achieve CR/CRi typically have a poor outcome and shortened overall survival. The ESC considered that patients who do not undergo a HSCT or who relapse following HSCT will likely cycle through the available therapies until remission or death.
- 4.4 The PBAC noted that inotuzumab and blinatumomab have different mechanisms of action. Inotuzumab is an antibody-drug conjugate composed of an anti-CD22 antibody covalently bound to a toxin. As an anti-CD22 antibody, it targets B-cells including nearly all B-lineage ALL. On the other hand, blinatumomab is a bispecific T cell engager antibody construct that selectively binds with high affinity to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells).

5 Comparator

- 5.1 The submission nominated blinatumomab as the main comparator. The main arguments provided in support of this nomination were that blinatumomab has become the standard of care treatment for patients with relapsed/refractory Ph- B-ALL; blinatumomab has a PBS listing for relapsed/refractory Ph- B-ALL; the place in therapy of inotuzumab is similar to that of blinatumomab; and blinatumomab is the medicine most likely to be replaced by inotuzumab in clinical practice.
- 5.2 The evaluation and the ESC considered that blinatumomab is the appropriate main comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the clinical need for effective therapies for relapsed or refractory B-ALL, and the potential for cure if patients go on to receive an allogeneic HSCT. The clinician outlined the higher rates of VOD associated with inotuzumab, but noted this was a known risk associated with HSCT and there were some modifiable risk factors. The clinician also advised that approximately 50% of patients would be hospitalised for administration of inotuzumab.
- 6.2 The clinician outlined that, if sequential use were allowed, many clinicians would use blinatumomab first due to the risk of VOD with inotuzumab. The patient groups for whom inotuzumab may be used in preference to blinatumomab included patients without high risk factors for liver disease but with: CNS disease, prior failure with blinatumomab, loss of CD19 on ALL cells, Philadelphia chromosome positive disease, or with social factors that make hospital admission for blinatumomab administration difficult.
- 6.3 The clinician outlined that there may be important benefits of inotuzumab in patients with Philadelphia chromosome positive disease, particularly given it was generally associated with a poorer prognosis, however the sponsor confirmed that listing had not been requested in this group of patients in this application.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from a health professional via the Consumer Comments facility on the PBS website. The comments described the benefits of inotuzumab for patients with very high risk childhood ALL primarily as a bridge to HSCT.

Clinical trials

6.5 The submission was based on an indirect comparison of inotuzumab (INO-VATE ALL trial) and blinatumomab (TOWER trial) in relapsed/refractory Philadelphia chromosome negative B-cell precursor acute lymphoblastic leukaemia, using standard of care chemotherapy as a common reference. An anchored matching-adjusted indirect comparison (MAIC) and a supporting/supplementary anchored simulated treatment comparison (STC) were also presented. The methodology, approach and results of the STC analysis were similar to the MAIC.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
INO-VATE ALL (B1931022) (NCT01564784)	An open-label, randomised phase 3 study of inotuzumab ozogamicin compared to a defined investigator's choice in adult patients with relapsed or refractory CD22 positive acute lymphoblastic leukaemia (ALL). Kantarjian H, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukaemia. Kantarjian H, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Kantarjian H, et al. Patient-reported outcomes from a phase 3 randomized controlled trial of inotuzumab ozogamicin versus standard therapy for relapsed/refractory acute lymphoblastic leukemia. Jabbour E.J. et. al. Efficacy and Safety Analysis by Age Cohort of Inotuzumab Ozogamicin in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia Enrolled in INO-VATE. Stelljes M. et al., 2017. Indirect treatment comparison (ITC) of inotuzumab ozogamicin (InO) and blinatumomab (Blina) for relapsed or refractory (RR) acute lymphoblastic leukemia (ALL).	7 October 2016. New England Journal of Medicine 2016; 375 (8):740-753. The Lancet Haematology 2017; 4(8):e387-e398. Cancer 2018 Mar 6. [Epub ahead of print] Cancer 2018 Jan 30 [Epub ahead of print] Blood 2017. 130 (Suppl-1):2558.
TOWER (NCT02013167)	Kantarjian H, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukaemia.	New England Journal of Medicine 2017; 376:836-847.
Supportive studies for inotuzumab		
B1931010 (NCT01363297)	An open-label, phase 1/2 study of inotuzumab ozogamicin in subjects with relapsed or refractory CD22 positive acute lymphocytic leukaemia.	31 October 2016.
2009-0872 (NCT01134575)	Kantarjian H, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Kantarjian H, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukaemia.	Lancet Oncology 2012; 13(4):403–411. Cancer 2013; 119(15):2728 – 2736.

Trial ID	Protocol title/ Publication title	Publication citation
Supportive studies for blinatumomab		
MT103-206 (NCT01209286)	<p>Topp MS, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory b-precursor acute lymphoblastic leukaemia.</p> <p>Zugmaier G, et al. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment.</p>	<p>Journal of Clinical Oncology 2014; 32(36):4134-4142.</p> <p>American Society of Hematology 2015; 126 (24): 2578 – 2584.</p>
MT103-211 (NCT01466179)	Topp MS et al. Safety and activity of blinatumomab for adult patient with relapsed or refractory B-precursor acute lymphoblastic leukaemia: A multicentre, single-arm, Phase 2 study.	Lancet Oncology 2015; 16; 57-66.

Source: Table 2.2.1, pp.63-66 of the submission.

Abbreviations: MRD, minimal residual disease.

6.7 The key features of the randomised trials included in the submission are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design	Risk of bias	Intervention	Patient population	Outcomes
Inotuzumab trial						
INO-VATE ALL	109/109 (ITT-218 ^a) 164/162 (ITT) 164/162 (LPLV)	Phase III, open label, randomised, controlled, multicentre, international trial	High	<u>Inotuzumab</u> : IV infusion, 1.8 mg/m ² per cycle, ^b 0.8 mg/m ² on Day 1 0.5 mg/m ² on Day 8 and Day 15. First cycle 21 days, then 28 days, treatment free Day 16 to Day 28. Maximum of 6 cycles. <u>SOC chemotherapy</u> : Investigator's choice of FLAG, MXN/Ara-C, or HiDAC.	Relapsed/refractory CD22 positive, B-ALL, ≥ 18 years. Eligible for first or second line salvage therapy. ^c ECOG ≤ 2.	Rate of complete remission or complete remission with incomplete haematological recovery. Overall survival; Progression free survival. Duration of response; HSCT rate. EQ-5D, EORTC-QLQ-C30. Safety.
Blinatumomab trial						
TOWER	271/134 ITT	Phase III, open label, randomised, controlled, multicentre, international trial	High	<u>Blinatumomab</u> : IV continuous infusion over 28 days followed by 14 days treatment free interval. 9 mcg/m ² /day for the first 7 days of Cycle 1, then 28 mcg/m ² /day for remainder of Cycle 1 and all subsequent cycles. Maximum of 4 cycles. <u>SOC chemotherapy</u> : Investigator's choice of FLAG-IDA, HiDAC; high-dose methotrexate; or clofarabine.	Relapsed/refractory Ph- B-ALL, ≥ 18 years, Eligible for salvage therapy following: induction therapy; relapse from first remission if duration ≤ 12 months; second or subsequent remission; or remission following HSCT. > 5% blasts in bone marrow. ECOG ≤ 2.	Overall survival. Rate of complete remission or complete remission with partial or incomplete haematological recovery. Relapse free survival. Event free survival. MRD rate; HSCT rate. EORTC-QLQ-C30.

Source: Table 2.2.2, pp.72-74 of the submission.

Abbreviations: B-ALL, B-cell precursor acute lymphoblastic leukaemia; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D, EuroQoL-5 dimension questionnaire; FLAG, fludarabine, cytarabine (Ara-C) and granulocyte-colony stimulating factor; FLAG-IDA, fludarabine, cytarabine (Ara-C), granulocyte-colony stimulating factor and idarubicin ; HiDAC, high-dose cytarabine; HSCT, haematopoietic stem cell transplantation; LPLV, last patient last visit; MRD, minimal residual disease; MXN/Ara-C, mitoxantrone and cytarabine; Ph-, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive; SOC, standard of care (chemotherapy); TKI, tyrosine kinase inhibitor.

^a Results from 3 populations/time-points were reported in the INO-VATE ALL trial: (1) the ITT-218 population was the primary outcome, and was based on the first 109 patients in each arm; (2) the full ITT population; and (3) the LPLV which included data from the ITT population collected post-hoc, after all patients had discontinued treatment.

^b Dose reduced to 1.5 mg/m² per cycle if complete remission or complete remission with incomplete haematological recovery achieved.

^c Ph+ patients must have failed treatment with at least one second or third generation TKI and standard multi-agent induction chemotherapy.

6.8 The ESC noted that both trials were open-label and considered this was reasonable given the distinctive adverse event profiles of the therapies. The submission acknowledged that the open label designs of the INO-VATE ALL and TOWER trials allowed for outcomes to be affected by participant or investigator knowledge of treatment allocation. The evaluation considered that the open label design of the

trials also allowed for treatment options to be influenced by treatment allocation (e.g. HSCT), and may have influenced decisions around treatment continuation. Treatment discontinuations prior to the first dose of trial drug in both trials were substantially larger in the standard of care chemotherapy treatment arm compared to the inotuzumab or blinatumomab treatment arms. The ESC considered that high drop-out rates in standard of care chemotherapy arms are expected in this condition.

- 6.9 In both the INO-VATE ALL and TOWER trials, protocol-specified therapy was discontinued at any time after the first treatment cycle on progression to HSCT. Suitability for HSCT was not determined by pre-specified criteria, but was investigator determined on a patient-by-patient basis, and was dependent on availability of a suitable donor. The ESC considered that this was appropriate and reflective of clinical practice. Patients progressing to HSCT were included in the analyses.
- 6.10 The PBAC noted that both the INO-VATE ALL and TOWER trials had stopped after meeting pre-specified stopping criteria, and the median duration of follow-up was 33 months in the INO-VATE ALL trial; and 11.7 months in the TOWER trial. As such, the PBAC noted that no further more mature results would be available from either trial.
- 6.11 The table below outlines some of the differences in baseline characteristics between patients in the INO-VATE ALL and TOWER trials.

Table 4: Baseline demographic and disease characteristics of participants in INO-VATE ALL and TOWER

	INO-VATE ALL (ITT)		TOWER (ITT)	
	Inotuzumab	SOC	Blinatumomab	SOC
N	164	162	271	134
Age, years				
mean (SD)	45.9 (17.07)	46.0 (16.60)	40.8 (17.1)	41.1 (17.3)
median	46.5	47.5	37.0	37.0
Gender male, n (%)	91 (55.5%)	102 (63.0%)	162 (59.8%)	77 (57.5%)
Race, n (%)				
Caucasian	112 (68.3%)	120 (74.1%)	228 (84.1%)	112 (83.6%)
Asian	31 (18.9%)	24 (14.8%)	19 (7.0%)	9 (6.7%)
African American	4 (2.4%)	3 (1.9%)	5 (1.9%)	3 (2.2%)
Other	17 (10.4)	15 (9.3%)	19 (7.0%)	10 (7.5%)
Site region, n (%)				
Europe	61 (37.2%)	66 (40.7%)	180 (66.4%)	85 (63.4%)
US or Canada	75 (45.7%)	79 (48.8%)	41 (15.1%)	23 (17.2%)
Other	28 (17.1%)	17 (10.5%)	50 (18.5%)	26 (19.4%)
Ph +, n (%)	22 (13.4%)	28 (17.3%)	0	0
Salvage phase, n (%)				
First	111 (67.7%)	104 (64.2%)	114 (42.1%)	65 (48.5%)
Second	51 (31.1%)	57 (35.2%)	91 (33.6%)	43 (32.1%)
Third	0	0	45 (16.6%)	16 (11.9%)
Fourth or later	0	0	21 (7.8%)	10 (7.4%)
Not known	2 (1.2%)	1 (0.6%)	NR	NR
Duration of first remission <12 mths, n (%)	98 (56.8%)	108 (66.7%)	109 (40.2%)	49 (36.6%)
Maximum central/local bone marrow blasts ≥ 50% (%)	66.5%	69.8%	77.6%	74.2%
Platelets (10 ⁹ /L) mean (SD)	80.0 (71.0)	81.8 (72.2)	93.5 (96.6)	71.6 (66.9)
Previous SCT, n (%)	29 (17.7%)	32 (19.8%)	94 (34.7%)	46 (34.3%)
Primary refractory, n (%)	27 (16.5%)	32 (19.8%)	46 (17.0%)	27 (20.1%)
Refractory to salvage, n (%)	28 (17%)	30 (19%)	87 (32.1%)	34 (25.4%)

Source: Table 2.4.2, p.97 of the submission; Kantarjian et al. 2017; Table 5, pp.20-22 of the MAIC and STC Technical Report, Appendix 4. Abbreviations: ITT, intention-to-treat; NR, not reported; Ph+, Philadelphia chromosome positive; SCT, stem cell transplant; SD, standard deviation.

- 6.12 Overall, there were differences between the characteristics of patients enrolled in the blinatumomab and inotuzumab studies in terms of Philadelphia chromosome expression, baseline risk (e.g. peripheral blast counts), disease status (e.g. number of prior salvage therapies and the proportion of patients with a prior HSCT) and the duration of first remission.
- 6.13 The evaluation considered that the blinatumomab studies included patients with a worse prognosis compared to the inotuzumab studies. However, the ESC considered that many of the differences were unlikely to be treatment effect modifiers. The ESC considered that the key differences likely to have an impact were that the TOWER (blinatumomab) trial included patients post-second line salvage therapy (who would likely have a worse prognosis) and patients with a longer duration of first remission (who would likely have a more favourable prognosis). The ESC considered that the overall direction of bias was difficult to determine but unlikely to be large with some factors favouring blinatumomab and others favouring inotuzumab.

- 6.14 The PBAC agreed with the evaluation and considered that the TOWER (blinatumomab) trial included patients with a worse prognosis because it included patients in third or later salvage, more patients who were refractory to prior salvage therapy and more patients with a previous HSCT. The PBAC considered that these three factors would likely confound the indirect comparison and favour inotuzumab.
- 6.15 Chemotherapy regimens used in the standard of care treatment arms varied between the TOWER and INO-VATE ALL trials, but the evaluation considered that more aggressive chemotherapy may have been used in the TOWER trial consistent with a younger population with more progressed disease. Chemotherapy treatment regimens used in the standard of care treatment arms in both trials also varied by site and investigator's discretion.
- 6.16 The primary outcomes of the INO-VATE ALL trial were complete remission and overall survival, and the primary outcome of the TOWER trial was overall survival. The submission acknowledged differences between the INO-VATE ALL and TOWER trials in terms of outcomes reported and definitions for complete remission (CR), progression free survival and HSCT rate (these differences are discussed further below for each relevant outcome).
- 6.17 The MAIC used individual patient data from the INO-VATE ALL trial (inotuzumab) to match baseline summary statistics reported from the TOWER trial (blinatumomab). A list of potential treatment effect modifiers was identified for each outcome from available baseline patient and disease characteristics, using results from the literature, stratified analyses in the INO-VATE ALL and TOWER trials (not provided for evaluation), and clinical expert opinion. The PBAC considered that the stratified analyses would have been informative and should have been included in the submission.

Table 5: Treatment effect modifiers by outcome identified in the submission

Outcome	Restricted set of potential modifiers	Full set of potential modifiers
Overall survival Event free survival	Age; Philadelphia chromosome status; prior HSCT; hepatic comorbidities; region.	[REDACTED]
Complete remission rates (CR/CRi)	Age; Philadelphia chromosome status; prior HSCT; duration of first remission (< 12 months); prior number of salvage therapies; maximum of central/local bone marrow blast (< 50% and ≥ 50%).	-
HSCT rate	Age; prior HSCT; region.	-
Adverse events	[REDACTED]	-

Source: Table 2.6.3, p.212 of the submission; Table 6, p.24 of the MAIC and STC Technical Report, Appendix 4 to the submission.
Abbreviations: CR, complete remission; CRi, complete remission with incomplete haematological recovery; HSCT, haematopoietic stem cell transplant.

- 6.18 Baseline patient and disease characteristics considered to be treatment effect modifiers were presented for the INO-VATE ALL populations before and after matching to the TOWER trial population for each outcome and were the same or similar between trials after weighting. However, the remaining sample sizes of the INO-VATE ALL matched datasets were small (< [REDACTED] % in overall survival full covariate set; < 50% in overall survival restricted covariate set). Patient characteristics before and after weighting were only reported for the identified treatment effect modifiers (i.e. thus it was not possible to determine: whether each individual potential effect modifier had an unexpected effect on the matching; or whether there were differences between samples in terms of unknown/unidentified treatment effect modifiers). Confounding of other trial characteristics and the applicability of the matched samples to the Australian setting could not be assessed.
- 6.19 The PBAC noted that the MAIC analysis did not adjust for the TOWER trial including more patients who were refractory to prior salvage therapy, and also could not adequately adjust for the inclusion of third and later salvage in the TOWER trial (it only rebalanced the inotuzumab sample for the distribution of patients in first and second salvage, but could not adjust for the TOWER trial including patients in third or later salvage). The PBAC considered that these two factors would likely confound the MAIC analysis and favour inotuzumab.
- 6.20 To account for potential violation of the proportional hazard assumption due to differences in short term and long term performance against standard of care chemotherapy, and in addition to standard analyses, time-dependent Cox regression (< 15 months or ≥ 15 months), and restricted mean survival time (RMST) analyses were used to quantify differences in overall survival and event free survival treatment effect

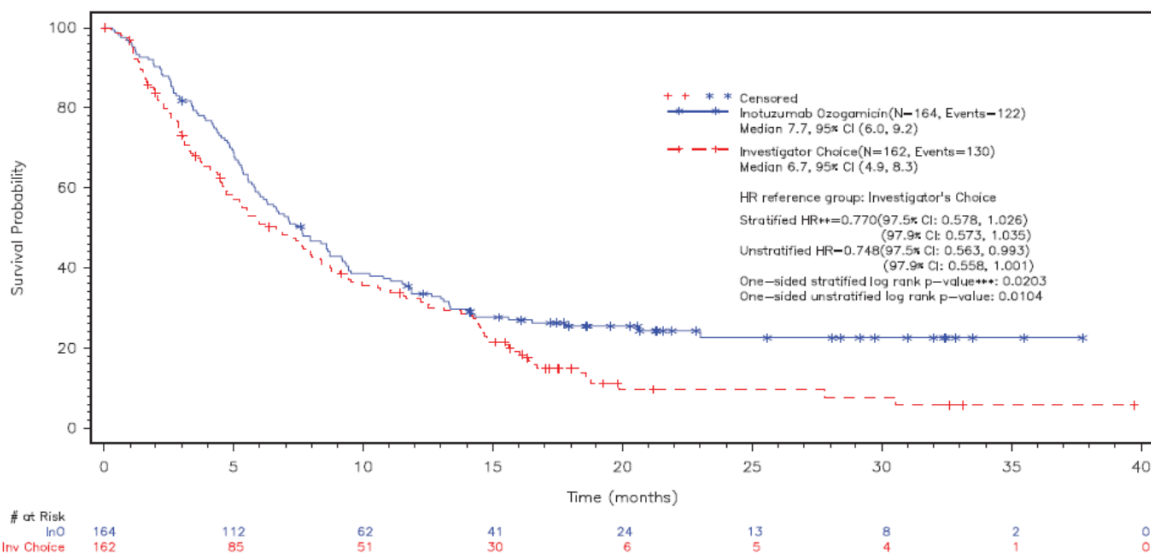
in the indirect comparisons. The truncation time for the event free survival RMST analysis was not adequately justified.

- 6.21 Non-inferiority margins for the key outcomes were not identified. The submission suggested that absence of statistically significant difference could be equated with non-inferiority in comparative analyses. However, the evaluation considered that the lack of a statistically significant difference is not a robust method for determining non-inferiority, as the wide confidence intervals may not exclude clinically important differences.

Comparative effectiveness

- 6.22 Figure 1 summarises the results for overall survival in the INO-VATE ALL trial, in the ITT population at the 8 March 2016 data cut.

Figure 1: INO-VATE ALL Kaplan-Meier plot of overall survival (ITT)



Source: Figure 2.5.3, p.135 of the submission.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

Note: Investigator's choice refers to standard of care chemotherapy.

- 6.23 Median overall survival was 7.7 months for inotuzumab and 6.7 months for standard of care chemotherapy for the ITT population. The hazard ratio for the difference in overall survival between the inotuzumab and standard of care chemotherapy (ITT population) was not statistically significant as the p value of 0.0203 (stratified log-rank test, 1-sided) exceeded the pre-specified 1-sided p-value boundary of 0.0104 (adjusted for interim analyses).

- 6.24 The PSCR stated that the overall survival curves reported in the INO-VATE study violate the proportional hazards assumption, with minimal differences observed during the early study period, followed by separation of the survival curves later in the study period (i.e. after 15 months). The PSCR referred to an exploratory post hoc analysis of

RMST (as outlined in Paragraph 6.20) which it stated had found that restricted mean overall survival was statistically significantly longer in the inotuzumab group versus the standard of care chemotherapy group.

- 6.25 The indirect analysis was based on the last patient last visit (LPLV) updated dataset (4 Jan 2017) rather than the ITT population of the INO-VATE ALL trial. This was a post hoc analysis undertaken after all patients had permanently discontinued from the trial.
- 6.26 Table 6 summarises the overall survival outcomes from the INO-VATE ALL and TOWER trials, and the results of the indirect comparisons, including the MAICs. Two MAIC analyses were presented, based on a restricted set of potential treatment effect modifiers (restricted set); and based on a full set of potential treatment effect modifiers (full set).

Table 6: Indirect comparison of overall survival – inotuzumab versus blinatumomab (standard of care chemotherapy as common reference)

Trial (analysis)	Inotuzumab	SOC chemotherapy	Blinatumomab	HR (95% CI)
Formal indirect analysis median survival (95% CI)				
INO-VATE ALL (LPLV), months (95% CI)	N=164 7.66 (6.01, 9.17)	N=162 6.21 (4.73, 8.35)	-	0.75 (0.59, 0.96)
TOWER (ITT), months (95% CI)	-	N=134 4.0 (2.9, 5.3)	N=271 7.7 (5.6, 9.6)	0.71 (0.55, 0.93)
Indirect analysis of inotuzumab vs. blinatumomab				1.06 (0.73, 1.52)
MAIC (INO-VATE ALL restricted set) median survival (95% CI)				
INO-VATE ALL (MAIC restricted set), months (95% CI)	N=83 7.95 (6.14, 10.78)	N=75 7.43 (3.78, 9.99)	-	0.68 (0.47, 0.97)
TOWER (ITT), months (95% CI)	-	N=134 4.0 (2.9, 5.3)	N=271 7.7 (5.6, 9.6)	0.71 (0.55, 0.93)
Matching adjusted indirect analysis of inotuzumab vs. blinatumomab (INO-VATE ALL restricted set)				0.96 (0.61, 1.50)
MAIC (INO-VATE ALL full set) median survival (95% CI)				
INO-VATE ALL (MAIC full set), months (95% CI)	N=83 7.95 (6.14, 10.78)	N=75 7.43 (3.78, 9.99)	-	0.68 (0.47, 0.97)
TOWER (ITT), months (95% CI)	-	N=134 4.0 (2.9, 5.3)	N=271 7.7 (5.6, 9.6)	0.71 (0.55, 0.93)
Matching adjusted indirect analysis of inotuzumab vs. blinatumomab (INO-VATE ALL full set)				0.96 (0.61, 1.50)

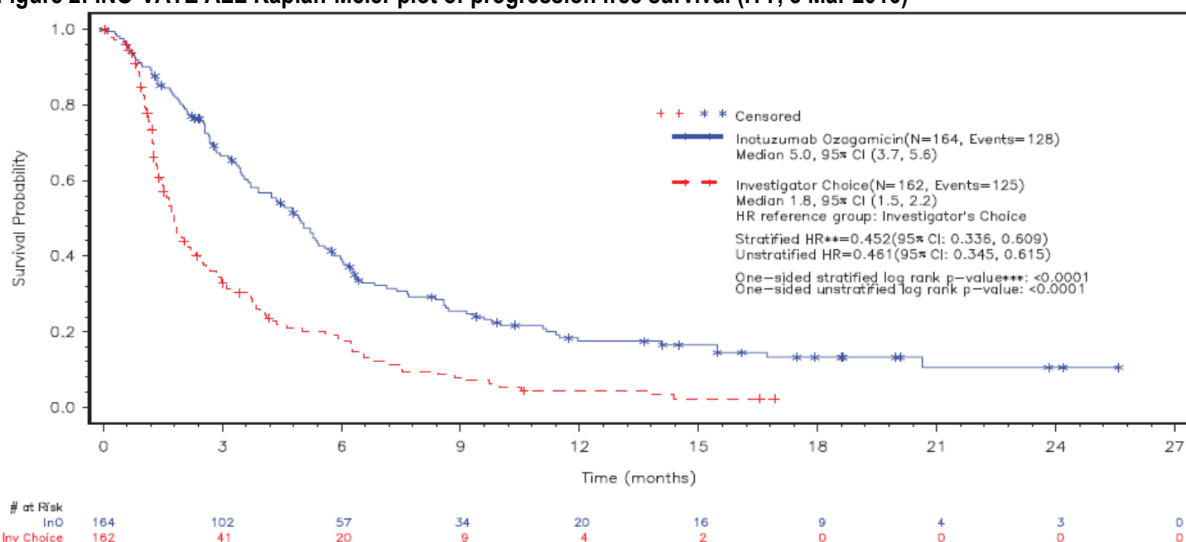
Source: Tables 2.6.4-2.6.5, p.220-221 of the submission.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LPLV, last patient last visit; MAIC, matching adjusted indirect comparison; SOC, standard of care chemotherapy.

- 6.27 For overall survival, the comparisons with standard of care chemotherapy generally statistically significantly favoured inotuzumab (INO-VATE ALL) and blinatumomab (TOWER). Results in the INO-VATE ALL trial were more favourable to inotuzumab in the anchored MAIC (restricted covariate) analysis compared to the LPLV dataset. In the TOWER trial, median survival for the standard of care chemotherapy treatment arm (4.0 months) was substantially shorter than reported for standard of care in the INO-VATE ALL trial (6.2 months), indicating that the common reference (standard of care chemotherapy) may not have been sufficiently similar between trials and/or that there were imbalances in prognostic factors.

- 6.28 In the indirect comparisons for overall survival, there were no statistically significant differences between inotuzumab and blinatumomab across all analyses. The evaluation considered that the lack of a statistically significant difference between treatments may not adequately justify a claim of non-inferiority given the wide confidence intervals, which indicate substantial uncertainty around the indirect estimates of effect.
- 6.29 In order to achieve long-term survival, patients with this condition generally require a HSCT, and the ESC noted there were higher rates of CR/CRi and subsequent HSCT in the inotuzumab INO-VATE ALL trial compared with the blinatumomab TOWER trial (HSCT rates of 48% versus 24% in the inotuzumab and blinatumomab arms, respectively as outlined in Table 9). The ESC considered that the differential rates of HSCT were likely to have affected the comparative estimates of overall survival.
- 6.30 The PBAC re-iterated its previous view, from its July 2016 consideration of blinatumomab for this condition, that overall survival is the most relevant outcome to inform decision-making (Blinatumomab Public Summary Document, July 2016). In particular, the PBAC considered that long-term improvements in survival were particularly relevant and noted that the proportion of patients with likely long-term survival (represented in the survival curves as a plateau) for inotuzumab in the INO-VATE ALL trial and blinatumomab in the TOWER trial were similar, at around 25%.
- 6.31 Figure 2 shows the Kaplan Meier plot of progression free survival (PFS) for the INO-VATE ALL ITT population. The definition of PFS in the INO-VATE ALL trial was not conventional as it included starting new induction therapy or post-therapy HSCT without achieving CR/CRi, in addition to death or disease progression.

Figure 2: INO-VATE ALL Kaplan-Meier plot of progression free survival (ITT, 8 Mar 2016)



Source: Figure 2.5.12, p.149 of the submission.

Abbreviations: CI, confidence interval; ITT, intention-to-treat.

Note: Investigator's choice refers to standard of care chemotherapy.

- 6.32 Median PFS was 5.0 months for inotuzumab and 1.8 months for standard of care chemotherapy. Deaths and relapse represented a larger proportion of first events for inotuzumab compared to standard of care chemotherapy, with new therapy or HSCT representing a higher proportion of first events in the standard of care chemotherapy arm. Given the open label design of the INO-VATE ALL trial and the risk of treatment allocation influencing patient progression to alternative treatment regimens, the evaluation considered that this result may not be reliable. The ESC further considered that the PFS may not be reliable due to the unconventional definition of PFS that was used in the INO-VATE ALL trial.
- 6.33 PFS was not assessed in the TOWER trial. The closest outcome available in TOWER was event-free survival (EFS). Given the unconventional definition of PFS used in the INO-VATE ALL, an alternative sensitivity PFS reported in the INO-VATE ALL trial (not provided for evaluation) was used in the indirect analyses, as it was claimed to have a definition more consistent with EFS in the TOWER trial.
- 6.34 Table 7 summarises the EFS outcomes from the INO-VATE ALL trial (using the sensitivity PFS outcome outlined above) and the TOWER trial, and the results of the indirect comparisons, including the MAICs.

Table 7: Indirect comparison of median event-free survival – inotuzumab versus blinatumomab (standard of care chemotherapy as common reference)

Trial (analysis)	Inotuzumab (sensitivity PFS)	SOC chemotherapy	Blinatumomab (event free survival)	HR (95% CI)
Formal indirect analysis median event-free survival (95% CI)				
INO-VATE ALL (LPLV)	N=164 Not estimable	N=162 Not estimable	-	0.47 (0.36, 0.60)
TOWER (ITT)	-	N=134 Not estimable	N=271 Not estimable	0.55 (0.43, 0.71)
Indirect analysis of inotuzumab vs. blinatumomab				0.85 (0.60, 1.20)
MAIC (INO-VATE ALL restricted set) median event-free survival (95% CI)				
INO-VATE ALL (MAIC restricted set)	N=83 Not estimable	N=75 Not estimable	-	0.40 (0.28, 0.57)
TOWER (ITT)	-	N=134 Not estimable	N=271 Not estimable	0.55 (0.43, 0.71)
Matching adjusted indirect analysis of inotuzumab vs. blinatumomab (INO-VATE ALL restricted set)				0.73 (0.47, 1.13)
MAIC (INO-VATE ALL full set) median event-free survival (95% CI)				
INO-VATE ALL (MAIC full set)	N= [redacted] [redacted]	N= [redacted] [redacted]	-	[redacted] ([redacted], [redacted])
TOWER (ITT)	-	N=134 Not estimable	N=271 Not estimable	0.55 (0.43, 0.71)
Matching adjusted indirect analysis of inotuzumab vs. blinatumomab (INO-VATE ALL full set)				[redacted] ([redacted], [redacted])

Source: Table 2.6.6-2.6.7, p.225-226 of the submission.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LPLV, last patient last visit; MAIC, matching adjusted indirect comparison; PFS, progression free survival; SOC, standard of care chemotherapy.

- 6.35 For EFS, the comparisons with standard of care chemotherapy statistically significantly favoured inotuzumab (INO-VATE ALL) and blinatumomab (TOWER) in all analyses. The INO-VATE ALL EFS comparisons based on the sensitivity PFS data were not presented

in the submission and could not be evaluated. However, results of the sensitivity PFS ITT comparison with standard of care chemotherapy appeared similar to those reported for the INO-VATE ALL ITT comparison presented in Figure 2.

- 6.36 In the indirect comparisons for EFS, there was no statistically significant difference between inotuzumab and blinatumomab in the formal indirect and anchored MAIC analyses. The evaluation considered that this result should be interpreted with caution because the lack of a statistically significant difference may not adequately justify a claim of non-inferiority, and there was uncertainty around the definition of PFS in the INO-VATE ALL trial data (sensitivity PFS).
- 6.37 Table 8 summarises the complete remission outcomes (CR/CRi/CRh) from the INO-VATE ALL and TOWER trials, and the results of the indirect comparisons, including the MAICs. Complete remission with partial hematologic recovery (CRh) was only reported in the TOWER trial and required a lower absolute neutrophil count (> 500/mcL) and platelets count (> 50,000/mcL) compared to complete remission with incomplete haematological recovery (CRi) reported in the INO-VATE ALL trial.

Table 8: Indirect comparison of complete remission rate (CR/CRi/CRh) – inotuzumab versus blinatumomab (standard of care chemotherapy as common reference)

Trial (analysis)	Inotuzumab	SOC chemotherapy	Blinatumomab	Odds Ratio (95% CI)
Complete remission rate (CR/CRi/CRh), n (%)				
INO-VATE ALL (LPLV)	N=164 121 (73.8%)	N=162 50 (30.9%)	-	6.3 (3.89, 10.21)
TOWER (ITT)	-	N=134 33 (24.6%)	N=271 119 (43.9%)	2.40 (1.50, 3.81)
Indirect analysis of inotuzumab vs. blinatumomab				2.63 (1.35, 5.12)
INO-VATE ALL (MAIC restricted set)	N=70 51 (72.4%)	N=53 15 (28.0%)	-	6.75 (3.04, 14.95)
TOWER (ITT)	-	N=134 33 (24.6%)	N=271 119 (43.9%)	2.40 (1.50, 3.81)
Matching adjusted indirect analysis of inotuzumab vs. blinatumomab (INO-VATE ALL restricted set)				2.81 (1.12, 7.05)

Source: Table 2.6.6-2.6.7, p.225-226 of the submission.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LPLV, last patient last visit; MAIC, matching adjusted indirect comparison; PFS, progression free survival; SOC, standard of care chemotherapy.

- 6.38 For complete remission rates, the comparisons with standard of care chemotherapy statistically significantly favoured inotuzumab (INO-VATE ALL) and blinatumomab (TOWER) in all analyses.
- 6.39 In the indirect comparisons for complete remission rates, the comparisons statistically significantly favoured inotuzumab compared to blinatumomab. Given the differences in the definition of complete remission between trials, and differences between trials in terms of disease severity and progression (salvage line of therapy), the evaluation considered that these results should be interpreted with caution.
- 6.40 Table 9 summarises the HSCT rates from the INO-VATE ALL and TOWER trials, and the results of the indirect comparisons, including the MAICs. HSCT rates in TOWER

included all patients progressing to HSCT based on investigator discretion. In the INO-VATE ALL trial, HSCT rate was based on investigator discretion but also required achieving complete remission (CR, CRi). Therefore, to make the outcome definition more similar between the trials, the submission presented a post hoc analysis which included all post-treatment HSCT observed in the INO-VATE ALL trial, regardless of treatment response or timing.

Table 9: Indirect comparison of HSCT rate – inotuzumab versus blinatumomab (standard of care chemotherapy as common reference)

Trial (analysis)	Inotuzumab	SOC chemotherapy	Blinatumomab	Odds Ratio (95% CI)
HSCT rate, n (%)				
INO-VATE ALL (LPLV)	N=164 79 (48.2%)	N=162 36 (22.2%)	-	3.25 (2.01, 5.26)
TOWER (ITT)	-	N=134 32 (23.9%)	N=271 65 (24.0%)	1.01 (0.62, 1.63)
Indirect analysis of inotuzumab vs. blinatumomab				3.23 (1.63, 6.40)
INO-VATE ALL (MAIC restricted set)	N=100 52 (51.5%)	N=94 19 (20.4%)	-	6.75 (3.04, 14.95)
TOWER (ITT)	-	N=134 32 (23.9%)	N=271 65 (24.0%)	1.01 (0.62, 1.63)
Matching adjusted indirect analysis of inotuzumab vs. blinatumomab (INO-VATE ALL restricted set)				4.11 (1.85, 9.12)

Source: Tables 2.6.10-2.6.11, p.229 of the submission.

Abbreviations: CI, confidence interval; HSCT, haematopoietic stem cell transplant; ITT, intention-to-treat; MAIC, matching adjusted indirect comparison; SOC, standard of care chemotherapy.

- 6.41 For HSCT rates the comparisons with standard of care chemotherapy statistically significantly favoured inotuzumab (INO-VATE ALL), but not blinatumomab (TOWER). Substantially larger proportions of patients in the inotuzumab arm of the INO-VATE ALL trial progressed to HSCT compared to standard of care chemotherapy, and both treatment arms of the TOWER trial.
- 6.42 The results of the indirect comparisons statistically significantly favoured inotuzumab. Given differences in HSCT rates between trials may be due to differences in selection criteria for progression to HSCT, trial populations, trial design or selection of patients for HSCT in open label trials the evaluation considered that these results should be interpreted with caution. However, the ESC noted that HSCT rates were similar in the standard of care chemotherapy arms between the two trials.
- 6.43 The ESC noted that inotuzumab was associated with a higher rate of HSCT than blinatumomab and considered that this was a clinically meaningful outcome that likely contributed to the overall survival and event free survival outcomes achieved with inotuzumab.
- 6.44 Overall, the PBAC agreed with the evaluation and considered that the comparison of HSCT rates between the two trials was difficult to interpret given the differences between the patient populations enrolled in the trials.

- 6.45 Quality of life outcomes were reported using EORTC QLQ-C30 and EQ-5D for the INOVATE ALL trial ITT population (8 March 2016 cutoff). There were no statistically significant differences in EQ-5D and EQ-VAS between patients treated with inotuzumab or standard of care chemotherapy. In the EORTC QLQ-C30 three functional and one individual scales showed statistically significant improvements for patients treated with inotuzumab compared to standard of care chemotherapy (physical functioning, role functioning, social functioning and appetite loss).
- 6.46 Quality of life outcomes were reported using EORTC QLQ-C30 in the TOWER trial. Mean changes in the global health scale, functional scales, and symptom scales of the EORTC QLQ-C30 questionnaire were minimal for blinatumomab compared to worsening scores for standard of care chemotherapy. Time to clinically meaningful deterioration in health related quality of life or death was delayed for blinatumomab compared to standard of care chemotherapy across all EORTC QLQ-C30 scales. Results were statistically significantly in favour of blinatumomab in all scales except social functioning, insomnia and financial difficulties.
- 6.47 The PBAC considered that these data indicated that blinatumomab may have been associated with more favourable changes in quality of life (based on EORTC QLQ-C30), than inotuzumab. However, the PBAC also noted that blinatumomab requires a set period of hospitalisation for administration, while hospitalisation for inotuzumab administration is not always required, dependent on patient characteristics.

Comparative harms

- 6.48 Table 10 summarises the key adverse events reported during the INOVATE ALL and TOWER trials.

Table 10: INO-VATE ALL and TOWER Summary of key adverse events in the randomised trials

Events	INO-VATE ALL		TOWER	
	Inotuzumab n (%)	SOC chemotherap y n (%)	Blinatumomab n (%)	SOC chemotherapy n (%)
N	164	143	267	109
Any adverse event (n (%) pts)	163 (99.4%)	143 (100.0%)	263 (98.5%)	108 (99.1%)
Number of serious adverse events	186	121	NR	NR
Serious adverse events (n (%) pts)	84 (51.2%) ^a	71 (49.7%)	165 (61.8%) ^a	49 (45.0%)
Grade 3 adverse events (n (%) pts)	147 (89.6%)	137 (95.8%)	98 (36.7%)	33 (30.3%)
Grade 4 adverse events (n (%) pts)			82 (30.7%)	48 (44.0%)
Fatal adverse events (n (%) pts)	26 (15.9%)	16 (11.2%)	51 (19.4%)	19 (17.4%)
Discontinued due to adverse event (n (%) pts)	30 (18.3%)	12 (8.4%)	33 (12.4%)	9 (8.3%)
Dose reduced due to adverse event (n (%) pts)	5 (3.0%)	3 (2.1%)	NR	NR
Treatment interrupted due to adverse event (n (%) pts)	72 (43.9%)	17 (11.9%)	86 (32.2%)	7 (6.4%)

Source: Tables 2.5.32, p.182 and 2.5.39, p.193 of the submission. Statistically significant results in bold.

Abbreviations: CI, confidence interval; pts, patients; SOC, standard of care

^a Included in the cost analysis, Sections 3 and 4 of the commentary.

- 6.49 In the INO-VATE and TOWER trials more than 98.5% of randomised patients reported adverse events in both treatment arms. Post-transplant mortality was similar in the inotuzumab and standard of care chemotherapy arms of the INO-VATE ALL trial (64.6% vs 65.7%). However, post-transplant non-relapse deaths were reported more frequently in patients in the inotuzumab arm compared to standard of care chemotherapy (40.5% vs 22.9%). The most common reasons for post-transplant non-relapse deaths in patients treated with inotuzumab compared to standard of care chemotherapy were infection (21.6% vs 17.4%) and veno-occlusive disease (VOD; 9.8% vs 0%).
- 6.50 The most frequently reported adverse events in the INO-VATE ALL trial were veno-occlusive disease/sinusoidal obstruction disease (VOD/SOS), febrile neutropenia and pneumonia. The most frequently reported adverse events in the TOWER trial were febrile neutropenia, neutropenia, sepsis, cytokine release syndrome and increased ALT.
- 6.51 In the INO-VATE ALL study, larger proportions of patients treated with inotuzumab developed VOD/SOS compared to standard of care chemotherapy (22/164 - 13.4% vs 1/162 - 0.7%). Five patients treated with inotuzumab who developed VOD/SOS died after HSCT within 42 days of the last dose of inotuzumab, and one after HSCT more than 42 days after the last dose (i.e. post-trial). While noting the rates of VOD/SOS were based on small patient numbers, the ESC considered the risk of VOD/SOS was concerning given the severity of the adverse event and the large absolute difference between the two arms. The ESC had requested that the sponsor provide, in its pre-PBAC response, any further information that is available about the risk of VOD/SOS.

- 6.52 The pre-PBAC response outlined the results of an analysis of the hepatotoxicity profile of inotuzumab (Kantarjian, 2017²) which suggested that the risk of VOD/SOS could be minimised by assessing patients for risk factors such as older age, prior HSCT, and history of liver disease, and also addressing modifiable risk factors such as minimising inotuzumab exposure before HSCT and avoiding conditioning regimens containing two alkylating agents. The study concluded that risks might be reduced through consideration of these risk factors and close monitoring for VOD/SOS.
- 6.53 The pre-PBAC response also provided a manuscript by McDonald, 2018³ which outlined an analysis of results from the expert panel who adjudicated hepatobiliary complications in the Phase 3 studies of inotuzumab in ALL and NHL. The study reported that SOS occurred in 5/328 (1.5%) patients receiving inotuzumab, versus no cases among 310 chemotherapy patients; and drug-induced liver injury occurred in 26 (7.9%) inotuzumab patients and 3 (1%) chemotherapy patients. Among patients with ALL who underwent HSCT, the frequency of SOS in the inotuzumab arms was 21/79 (27%) versus 3/34 (9%) in the chemotherapy arms. An exploratory multivariate model identified a past history of liver disease and thrombocytopenia before conditioning therapy as dominant risk factors for SOS after transplant.
- 6.54 The PSCR stated that in the inotuzumab arm of the INO-VATE ALL study, 8% of patients (13/164) received concomitant treatment with defibrotide, either for prophylaxis (n=2) or treatment of VOD (n=11). The PSCR further stated that defibrotide is not registered in Australia, and thus balance of benefit to risk has not been established.
- 6.55 The proportion of patients who experienced cytokine release syndrome in the TOWER trial was larger in the blinatumomab arm compared with standard of care chemotherapy arm for any grade adverse event (14.2% vs. 0%), grade ≥ 3 adverse events (4.9% vs. 0%) and for serious adverse events (2.6% vs. 0%).
- 6.56 The most commonly reported adverse events in the INO-VATE ALL trial were thrombocytopenia, neutropenia, infections and infestations, anaemia, nausea, pyrexia, leukopenia, headache and febrile neutropenia. In the TOWER trial, the most commonly reported adverse events were pyrexia, headache, anaemia, febrile neutropenia, diarrhoea, nausea, neutropenia, thrombocytopenia and fatigue.

² Kantarjian H et al, Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. *The Lancet Haematology*. 2017. 4(8), PE387-E398

³ McDonald G, et al. Liver complications following treatment of hematologic malignancy with anti-cd22-calicheamicin (Inotuzumab Ozogamicin). *Hepatology*. doi: 10.1002/hep.30222.

6.57 Table 11 summarises the results of an indirect analysis and anchored MAIC analysis for four selected adverse events presented in the submission.

Table 11: Indirect comparison in adverse events – inotuzumab versus blinatumomab (standard of care chemotherapy as common reference)

	Inotuzumab versus blinatumomab (SOC chemotherapy common reference)	
	Formal indirect analysis	Anchored MAIC
Infection Grade 3+ OR (95% CI)	()	()
Febrile neutropenia grade 3+ OR (95% CI)	()	()
Pyrexia OR (95% CI)	()	()
Fatal serious adverse events OR (95% CI)	()	()

Source: Table 2.6.13, p.233 of the submission.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MAIC, matching adjusted indirect comparison; SOC, standard of care chemotherapy.

6.58 In the indirect and the anchored MAIC comparisons, the rate of pyrexia was statistically significantly higher for blinatumomab compared to inotuzumab. All other comparisons showed no statistically significant differences between inotuzumab and blinatumomab. The submission noted that the results of the safety analyses should be interpreted with caution due to potential differences in standard of care chemotherapy regimens, and methods of defining, ascertaining and reporting adverse events between INO-VATE ALL and TOWER.

Benefits/harms

6.59 A benefits/harms summary was not presented for inotuzumab versus blinatumomab due to the claim of non-inferiority.

Clinical claim

6.60 The submission described inotuzumab as non-inferior in terms of effectiveness compared with blinatumomab and different but non-inferior in terms of safety compared to blinatumomab in the treatment of relapsed/refractory, Philadelphia chromosome negative, CD22-positive, B-cell precursor acute lymphoblastic leukaemia.

6.61 The evaluation considered that the clinical claim presented in the submission was not adequately supported.

- The results of the formal indirect comparison may not be reliable given the lack of exchangeability between the INO-VATE ALL and TOWER trials in terms of baseline patient characteristics, eligibility criteria, outcome definitions, disease progression criteria and standard of care chemotherapy regimens.
- The common reference (standard of care chemotherapy) may not have been sufficiently similar between trials to support the indirect comparisons.
- The MAIC may not be reliable given differences between the INO-VATE ALL and TOWER trials in terms of baseline patient characteristics and eligibility criteria

identified as treatment effect modifiers that could not be adequately adjusted for in the MAIC methodology.

- Covariates identified as potential treatment effect modifiers were not adequately tested for treatment effect or magnitude of effect. In addition, assessment of the effect of matching on baseline patient and disease characteristics in the INO-VATE ALL matched samples was not possible, as baseline disease and patient characteristics before and after matching were only presented for identified potential treatment modifiers (i.e. it was not clear if there were differences between samples in terms of unknown/unidentified treatment effect modifiers).
- The safety profiles of inotuzumab and blinatumomab both include severe potentially life threatening adverse events, but are distinctly different. Given the differences in standard of care chemotherapy regimens, and methods of defining, ascertaining and reporting adverse events between the INO-VATE ALL and TOWER trials, the evaluation considered that the indirect comparisons and informal assessments of safety outcomes are highly uncertain, and should be interpreted with caution.

- 6.62 The ESC noted the differences between trials, but considered the overall direction of bias was unlikely to be large, with some factors favouring blinatumomab and others favouring inotuzumab. Overall, the ESC considered that the claim of non-inferior effectiveness was adequately supported for the outcomes of event free survival and overall survival. The ESC considered that acceptance of non-inferiority was based on inotuzumab being associated with higher rates of CR/CRi and subsequent HSCT, but also higher rates of post-transplant non-relapse mortality.
- 6.63 The PBAC accepted that inotuzumab is superior to standard of care chemotherapy based on the data presented from the INO-VATE ALL trial.
- 6.64 The PBAC considered that the claim of non-inferior comparative effectiveness of inotuzumab versus blinatumomab was reasonable in the context of an uncommon disease where a direct randomised comparison would not be forthcoming.
- 6.65 The PBAC considered that the claim of different but non-inferior safety was reasonable.

Economic analysis

- 6.66 The submission presented a cost-minimisation analysis of inotuzumab versus blinatumomab, based on the claim of non-inferior effectiveness and different but non-inferior safety.
- 6.67 The submission estimated the equi-effective doses as: inotuzumab 9 x 1 mg vials over 2.7 cycles is equi-effective to blinatumomab 56 x 38.5 mcg vials over 1.64 cycles.
- 6.68 The equi-effective dose of inotuzumab was derived from the mean number of vials per course of treatment in the INO-VATE ALL trial. Patients progressing to HSCT or not

achieving CR or CRi within three cycles could continue treatment with inotuzumab in the INO-VATE ALL trial, which is inconsistent with the recommended dosing regimen in the inotuzumab Product Information. The submission therefore adjusted its calculation of the number of vials per patient to exclude vials used in Cycles 4-6 in patients progressing to HSCT or not achieving CR or CRi within three cycles. This adjustment reduced the average number of inotuzumab vials per patient from 9.3 in the trial to 9.0 with the submission's adjustment (which subsequently increased the price per vial). The evaluation considered that exclusion of inotuzumab dosing data from these patients (in Cycles 4-6) may not reflect clinical practice where some patients may continue treatment for longer than permitted under the PBS restriction. The PBAC also noted that the INO-VATE ALL efficacy data reflected the trial-based dosing. With the resubmission's adjusted approach the PBAC was uncertain whether cost-minimisation would be achieved. Therefore, the PBAC considered that, in this case, the trial-based dosing (which resulted in an average of 9.3 inotuzumab vials per patient) would be more appropriate for calculating the equi-effective dose of inotuzumab.

- 6.69 The submission derived the equi-effective dose of blinatumomab from the estimated total mean dose of blinatumomab described in the November 2016 blinatumomab Public Summary Document (i.e. 1,156 mcg as 42 vials of blinatumomab over an average treatment duration of 1.64 cycles) (Blinatumomab PSD, November 2016, para.6.12). However, the inotuzumab submission noted that the DPMA of blinatumomab in the January 2018 PBS Schedule increased by \$20,333.39 for Public hospitals and \$20,618.08 for Private hospitals, and assumed that this price increase was related to a revision of the number of vials of blinatumomab required to supply the listed maximum quantities, which it estimated would have added an additional 7 vials per cycle of treatment. Therefore, the submission recalculated the equi-effective dose of blinatumomab at 1,156 mcg as 56 vials (i.e. assuming 20.6 mcg per vial) of blinatumomab over an average treatment duration of 1.64 cycles.
- 6.70 The submission's assumption was not appropriate, and was corrected in the economic analysis and financial estimates presented below. The ex-manufacturer price spreadsheets⁴ show that the vial content for blinatumomab was amended from 39 mcg on 1 December 2017 to 28 mcg on 1 January 2018 (the spreadsheet also shows that the AEMP did not change). Thus, the mean dosage regimen of blinatumomab of 1,156 mcg over 1.64 cycles would require 42 vials, which is consistent with the mean number of vials reported in the blinatumomab Public Summary Document. Further, the blinatumomab Product Information (Table 3 of the Product Information, refer to footnotes a, b and c) outlines the number of vials required to prepare blinatumomab

⁴ Available at <http://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price>

infusions, with most of these requiring one vial per 24 hours, indicating that each 38.5 mcg vial of blinatumomab yields 28 mcg of the active agent.

- 6.71 Thus, the PBAC agreed the equi-effective doses should be: inotuzumab 9.3 x 1 mg vials is equi-effective to blinatumomab 42 x 28 mcg vials. Using these equi-effective doses, the results of the cost-minimisation analysis are summarised in Table 12, using the most recent dispensing fees.

Table 12: Results of the cost-minimisation analysis (based on published prices and the equi-effective doses that the PBAC considered were appropriate)

Component	CMA assuming 42 vials blinatumomab ^a	
	Inotuzumab	Blinatumomab
AEMP per vial	\$13,109.24	\$2,904.77
Mean vials per course of treatment	9.3	42 ^a
AEMP per mean course of treatment	\$121,915.90	\$122,000.34
DPMA per mean course of treatment	\$122,169.22	\$122,169.22

Source: Table 3.2.4, p.261 of the submission; Inotuzumab_Section 3_Pricing.xlsx, Attached to the submission, updated to reflect the equi-effective doses that the PBAC considered were appropriate.

Abbreviations: AEMP, approved ex-manufacturer price; CMA, cost minimisation analysis; DPMA, dispensed price for maximum amount.

^a Assuming 42 vials of blinatumomab for the average dose of 1,156 mcg over 1.64 cycles and assuming a public hospital dispensing fee of \$84.44.

- 6.72 The cost-minimisation analysis was based on drug costs only. The submission claimed, based on an analysis of costs, that the non-drug costs associated with inotuzumab treatment are likely to be no more than the costs associated with blinatumomab. The analysis included the costs of premedication, inpatient administration, hospitalisation for adverse events (using the average AR-DRG for ‘Acute leukaemia major complexity’), and managing adverse events of special interest. The evaluation and the ESC considered that it was unclear whether this claim was reasonable, given the submission’s analysis did not include all appropriate additional costs (e.g. outpatient administration), and underestimated the additional costs of inotuzumab (e.g. costs of pre-medication and adverse events). In particular, the ESC considered that the costs of treating VOD/SOS in the inotuzumab arm may have been underestimated (due to the uncertain duration of treatment with defibrotide and the use of average hospital costs).
- 6.73 The pre-PBAC response stated that the cost of defibrotide applied in the cost analysis was likely overestimated (and therefore conservative) because it was based on an average of [REDACTED] days of treatment, while the median duration of treatment with defibrotide in the INO-VATE ALL trial was [REDACTED] days, which the pre-PBAC response stated was consistent with advice received from the sponsor’s advisory board. The PBAC noted that it would have been more appropriate to use the mean duration of treatment, but overall considered that the non-drug costs associated with inotuzumab treatment are likely to be no more than the costs associated with blinatumomab.
- 6.74 The evaluation and the ESC considered that the estimated treatment effects (in terms of overall survival and event free survival) for inotuzumab in the INO-VATE ALL trial

and blinatumomab in the TOWER trial were affected by the use of HSCT. Thus, the evaluation and the ESC considered that the cost of HSCT should be included in the economic analysis as the clinical outcomes are based on the level of HSCT use in the clinical trials, and use of HSCT is a direct consequence of treatment with either inotuzumab or blinatumomab, with higher rates of HSCT having been reported with inotuzumab.

- 6.75 The PSCR stated that “HSCT is a consequence of the success of the previous treatment and is considered to be an independent treatment”. The PSCR further stated that the submission did not claim any benefit associated with the increased rate of HSCT with inotuzumab. However, the ESC considered that the rate of HSCT is reflected in the overall survival and event free survival outcomes observed in the two trials, and it is not possible to determine whether non-inferior OS and event free survival would have been achieved without the higher rate of HSCT observed in the inotuzumab trial.
- 6.76 The pre-PBAC response stated that a cost analysis that includes HSCT costs would also need to include the costs of any other subsequent treatments (i.e. it would need to include the corresponding cost offsets from cycling through other available therapies by patients who do not proceed to HSCT). The PBAC further considered that such a cost analysis would also need to include other costs, such as the costs of managing adverse events and sequential use.
- 6.77 The ESC considered that the full benefits and costs of the differential rates of subsequent HSCTs (and the potentially differential rates of post-transplant non-relapse mortality) may be more appropriately captured in a cost-utility analysis. The ESC considered that a cost-minimisation analysis may not be the most appropriate type of economic evaluation in this particular case because the adverse event profiles of inotuzumab and blinatumomab are different⁵; and if sequential use is permitted, then listing inotuzumab would be anticipated to result in higher costs to the health system particularly in light of the fixed-course nature of the treatments ⁶.
- 6.78 The pre-PBAC response claimed that such an analysis would rely on an uncertain incremental benefit (remission rate, HSCT rate and long term OS).

⁵ Page 95 of the *Guidelines for preparing a submission to the PBAC, Version 5.0, September 2016* states: “Irrespective of the therapeutic claim, if the adverse effect profiles of a proposed medicine and its main comparator are significantly different in nature, it is unlikely that the cost-minimisation approach will suffice. The implications of these differences, for both health outcomes (ideally, utility) and resource use, should be explored in a full economic evaluation.”

⁶ Page 60 of the *Guidelines for preparing a submission to the PBAC, Version 5.0, September 2016* states: “A cost-minimisation approach is appropriate where... the safety profile is equivalent or superior (in both nature and magnitude), and use of the proposed medicine is anticipated to result in equivalent or lesser costs to the health system.”

Drug cost/patient/course

6.79 The drug cost of inotuzumab (Public Hospital DPMA) per patient per average course of treatment is \$122,169, which is the same as the average cost of blinatumomab per patient per average course of treatment. These are based on published prices.

Estimated PBS usage & financial implications

6.80 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial implications associated with PBS listing of inotuzumab for the treatment of patients with relapsed or refractory Ph- CD22 positive B-ALL. Cost offsets were derived from substitution of blinatumomab (the comparator) in the market.

6.81 Table 13 summarises the estimated extent of use and costs of listing inotuzumab for the treatment of relapsed or refractory Ph- CD22 positive B-ALL in the first 6 years of listing.

Table 13: Estimated use and financial implications

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Eligible population with Ph- CD22+ relapsed / refractory B-cell precursor acute lymphoblastic leukaemia (B-ALL)						
Eligible population with relapsed / refractory Ph- CD22+ B-ALL	■	■	■	■	■	■
Estimated treatment uptake WITHOUT inotuzumab listed on the PBS (patients)						
Blinatumomab uptake (■%)	■	■	■	■	■	■
Other therapies uptake (■%)	■	■	■	■	■	■
Estimated treatment uptake WITH inotuzumab listed on the PBS (patients)						
Inotuzumab uptake (patients)	■	■	■	■	■	■
Number of inotuzumab 1 mg vials ^b	■	■	■	■	■	■
Estimated cost to the PBS (corrected during the evaluation for equi-effective dose of 42 vials of blinatumomab)						
Cost to PBS including copayment	■	■	■	■	■	■
Patient copayment (mean \$23.75)	■	■	■	■	■	■
Cost of inotuzumab to PBS less copayment	■	■	■	■	■	■
Estimated financial implications (corrected during evaluation for equi-effective dose of 42 vials of blinatumomab)						
Cost of inotuzumab to the PBS Less copayment	■	■	■	■	■	■
Cost offset to PBS of blinatumomab less copayment	■	■	■	■	■	■
Total cost of PBS listing inotuzumab less copayment	■	■	■	■	■	■

Source: Tables 4.2.1 to 4.2.9, pp.280-289 and Tables 4.3.2 to 4.3.4, pp.292-294 of the submission.

Abbreviations: ALL, acute lymphoblastic leukaemia; B-ALL, B-cell precursor acute lymphoblastic leukaemia; Ph-, Philadelphia chromosome negative.

^a Includes addition of ■ grandfathered patients.

^b Assumed 9 vials of inotuzumab over 3 cycles of treatment; i.e. dispensed 3 times (3 × [3 × 1 mg vial]).

Note: items in italics calculated during the evaluation.

The redacted table shows that at Year 6, the estimated number of patients was substantially less than 10,000 per year.

- 6.82 The cost to the PBS of listing of inotuzumab calculated during the evaluation (using the equi-effective dose of blinatumomab of 42 vials over 1.64 cycles) was estimated at less than \$10 million in the sixth year of listing, with a cumulative cost to the PBS over six years of \$10 - \$20 million (published prices). Including estimated cost offsets to the PBS due to substitution of blinatumomab, the overall financial implications to the PBS was estimated at less than \$10 million in the sixth year of listing, with a cumulative cost to the PBS over six years of less than \$10 million (published prices). The PBAC noted that these estimates did not include the additional costs associated with sequential use of inotuzumab and blinatumomab.
- 6.83 The submission assumed there would be ■% uptake from “other therapies” (in addition to assuming uptake from blinatumomab) in first salvage, as a small proportion of patients were assumed to be unsuitable or ineligible for blinatumomab. However, the evaluation considered that it was unclear which group/s of patients would be ineligible for blinatumomab but eligible for inotuzumab. The ESC considered that the most likely group would be those with CNS disease as this is not a contraindication for inotuzumab. However, the ESC and PBAC considered that this would only represent a very small number of patients, if any, as other therapies would be preferred for patients with CNS disease. As such, the PBAC considered that uptake from “other therapies” was likely to be <10% in first salvage.
- 6.84 The evaluation considered that it was unclear whether the claimed cost offsets associated with substitution of inotuzumab for blinatumomab would be realised in practice, given patients may use both blinatumomab and inotuzumab in different lines of treatment (i.e. sequential use in patients who do not undergo HSCT). The PBAC agreed that, with sequential use permitted, listing inotuzumab would be associated with additional costs to the PBS/RPBS.
- 6.85 The PBAC noted that sequential use would occur in: patients who relapse following a HSCT; or in patients who do not proceed to HSCT after first salvage. In estimating the increase in treatment courses that would occur with sequential use permitted, the PBAC noted the following data:
- 24% of patients in the blinatumomab arm of the TOWER trial, and 51.5% of patients in the inotuzumab arm of the INO-VATE ALL trial (MAIC analysis) received a HSCT, with the HSCT rate in the PBS population likely to be somewhere between these two figures noting the midpoint is 38%. (As outlined above, the PBAC considered that the comparison of HSCT rates between the two trials was difficult to interpret given the differences between the patient populations. Thus any weighting of the two HSCT rates between the trials would be unreliable. Further, it would be improbable for inotuzumab patients to constitute more than half this population.) The PBAC estimated that around 40% of patients who receive a HSCT

would relapse and be suitable for a second salvage (with this estimate based on its clinical expertise). Thus, around 15% of total patients would relapse following a HSCT and be suitable for second salvage.

- Based on the above, around 62% of PBS patients would not proceed to HSCT (i.e. because 38% of patients do proceed to HSCT). The PBAC estimated that around 50% to 60% of these patients would proceed to second salvage (with this estimate based on its clinical expertise). Thus, around 35% of total patients would not receive a HSCT and be suitable for second salvage.
- Overall, the PBAC considered that no more than 50% of patients would require sequential use of blinatumomab or inotuzumab (i.e. the number of courses of treatment with blinatumomab or inotuzumab would increase by no more than 50% with sequential use permitted).

6.86 Given it had recommended an amendment to the blinatumomab restriction to allow use in first- and second- salvage only, the PBAC considered that there may be a small decrease in the number of patients treated with blinatumomab (even if inotuzumab was not available). The PBAC considered that the impact would be minor given most incident patients would be treated now with blinatumomab (or inotuzumab) in first- or second- salvage and most prevalent patients in later salvage would have already been treated with blinatumomab. Further, the PBAC considered that any decrease in patient numbers as a result of this amendment would likely be offset by the amendment to the blinatumomab restriction to allow use in patients with an ECOG status of 2.

6.87 The evaluation considered that the estimated financial implications to the PBS of listing inotuzumab are highly uncertain for the following reasons:

- The eligible population only included patients with relapsed/refractory disease following first line therapy. Prevalent patients experiencing subsequent episodes of salvage therapy were excluded, underestimating the cost of inotuzumab to the PBS. Further, the ESC noted that the estimates did not include the potential for use in patients who relapse post-HSCT. The PBAC noted that its estimation of the increased number of treatment courses with sequential use would address some of these issues.
- The estimated uptake of inotuzumab and substitution of blinatumomab was assumed based on expert advice commissioned by the sponsor and is uncertain.

6.88 The evaluation and the PBAC considered that the following issues should be addressed:

- The estimated number of blinatumomab scripts likely to be substituted by inotuzumab was overestimated due to rounding up of weighted individual blinatumomab PBS item script numbers.

- The use of different approaches to estimate the costs of inotuzumab (averaged) and blinatumomab (disaggregated/re-aggregated), and the rounding up of blinatumomab use for each course of treatment to two full cycles was not justified, and resulted in overestimating the costs of blinatumomab.
- The different approaches used to estimate patient copayments for inotuzumab and blinatumomab were not justified. A single mean patient co-payment was deducted from the gross annual cost of inotuzumab over three cycles of treatment. Blinatumomab copayments were aggregated by PBS item.

Quality Use of Medicines

- 6.89 The submission noted that education material would be available for clinicians and patients in the form of Product Information and Consumer Medicines Information documents, further undefined educational programs for haematologists and nurses, a review paper of VOD risk assessment, diagnosis and management by a local expert haematologist, and published clinical guidelines (e.g. Australian EviQ Guidelines).

Financial Management – Risk Sharing Arrangements

- 6.90 The submission noted that blinatumomab is subject to a special pricing arrangement and may also be subject to an expenditure capped risk-sharing arrangement. The submission suggested that a special pricing arrangement and risk-sharing arrangement would be required for inotuzumab. The sponsor stated that it is willing to work with the Department of Health to finalise the details of suitable arrangements.

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 inotuzumab 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). The PBAC recommended the listing on a cost-minimisation basis against blinatumomab.
- 7.2 The PBAC considered that sequential use of inotuzumab and blinatumomab (in either order) would be clinically appropriate in some patients given the differing mechanisms of action and the clinical need for additional therapeutic options for patients who are unable to receive a HSCT or who progress after a HSCT. While acknowledging the lack of data available on the incremental effectiveness of adding a second agent, the PBAC considered there was a clinical place for sequential therapy given the poor prognosis of patients with relapsed/refractory B-ALL. The PBAC noted the clinician in the sponsor hearing supported sequential therapy, with the preferred order of sequencing being dependent on patient characteristics.

- 7.3 The PBAC noted that the submission did not seek listing in patients with Philadelphia chromosome positive disease and no economic or financial data were provided in the submission for this population. However, the PBAC considered there is a high clinical need in this patient group and noted that the INO-VATE ALL trial included patients with Philadelphia chromosome positive disease. As such, the PBAC advised that it would welcome a future submission for this patient group.
- 7.4 The PBAC considered that the restrictions for inotuzumab and blinatumomab should align where possible. In particular, the PBAC considered that the restriction for inotuzumab should: not specify an age restriction, include definitions of CR or CRi that align with those included in the blinatumomab restriction; and specify that it can only be used for one course per lifetime.
- 7.5 The PBAC considered that the restrictions for both inotuzumab and blinatumomab should allow use in patients with ECOG status of 2 or less, consistent with the inclusion criteria of the INO-VATE ALL and TOWER trials. The PBAC noted that this would require an amendment to the existing blinatumomab restriction which currently excludes patients with an ECOG status of 2.
- 7.6 The PBAC considered that the inotuzumab restriction should only allow use in first or second salvage, consistent with the inclusion criteria in the INO-VATE ALL trial. The PBAC noted that blinatumomab is currently subsidised for use in any line of salvage, but recalled that the impact of blinatumomab on OS was uncertain in third or later salvage. Thus, the PBAC considered that the PBS restriction for blinatumomab should be updated to allow use only in first and second salvage, consistent with the restriction recommended for inotuzumab, and in line with the population for whom the clinical evidence suggests there is likely to be the most benefit. The PBAC considered this change was necessary because, with a second agent available, the number of patients proceeding to third or later salvage will increase over time.
- 7.7 The PBAC considered that the inotuzumab restriction should differ from the blinatumomab restriction in that the inotuzumab restriction should: limit treatment to patients with CD22 expression (consistent with the inclusion criteria in the INO-VATE ALL); allow use in patients with disease present in the CNS or testes (consistent with the Product Information); and not specify the period of hospitalisation required for administration (while inotuzumab administration often requires hospitalisation, no set period is specified in the Product Information).
- 7.8 The PBAC considered that blinatumomab was the appropriate main comparator.
- 7.9 The PBAC considered that the TOWER (blinatumomab) trial included patients with a worse prognosis and who would be more difficult to treat because it included: patients in third or later salvage; more patients who were refractory to salvage; and more patients with a previous HSCT. The PBAC considered that these three factors would likely confound the analysis and favour inotuzumab.

- 7.10 Given these differences between the trial populations, the PBAC considered that it was difficult to interpret the CR, EFS and HSCT rates through an indirect comparison. In addition, the PBAC noted that the MAIC analyses could not adequately adjust for some of the key differences. The PBAC also noted the other limitations of the MAIC analysis including that the sample sizes of the INO-VATE ALL matched datasets were small, and that it was not possible to assess confounding of other trial characteristics or the applicability of the matched samples to the Australian setting. Overall, the PBAC considered that the MAIC analyses were informative but likely biased in favour of inotuzumab.
- 7.11 The PBAC considered that the proportion of patients with likely long-term survival (represented in the survival curves as a plateau) for inotuzumab and blinatumomab were similar, indicating similar effectiveness. Overall the PBAC accepted that inotuzumab has non-inferior comparative effectiveness versus blinatumomab.
- 7.12 The PBAC noted that inotuzumab was associated with higher rates of VOD/SOS compared with standard of care chemotherapy (13.4% versus 0.7%) in the INO-VATE ALL study. However, the PBAC also noted that blinatumomab was associated with higher rates of cytokine release syndrome compared with standard of care chemotherapy arm (14.2% versus 0% for any grade adverse event). Overall, the PBAC considered that inotuzumab was associated with different but non-inferior safety compared with blinatumomab.
- 7.13 The PBAC considered that the equi-effective doses of inotuzumab and blinatumomab are: inotuzumab 9.3 x 1 mg vials is equi-effective to blinatumomab 42x 28 mcg vials.
- 7.14 The PBAC noted that the cost-minimisation analysis did not include the cost of HSCT. The PBAC considered it would have been more appropriate to incorporate the full benefits and costs of the differential rates of subsequent HSCTs in the economic analysis because the clinical outcomes are based on the level of HSCT use in the clinical trials, and use of HSCT is a direct consequence of treatment with either inotuzumab or blinatumomab. However, the PBAC considered that the data to inform this comparison were not sufficiently reliable. In particular, the PBAC considered that the differential rates of HSCT observed in the INO-VATE ALL and TOWER trials were likely confounded by the differences in patient populations between the two trials. Thus, the PBAC considered that, in this case, it was appropriate for the cost-analysis to exclude HSCT costs. Further, the PBAC considered that the other non-drug costs associated with inotuzumab treatment are likely to be no more than the costs associated with blinatumomab. As such, the PBAC considered that the cost-minimisation analysis should be based on drug costs only.
- 7.15 The PBAC noted that, with sequential use, listing inotuzumab would result in higher costs to the health system. The PBAC considered the additional cost to be readily calculable based on the information presented in the submission, and would be contained given the small patient numbers. The PBAC considered that a cost-

minimisation analysis remained appropriate in this particular case given the cost-effectiveness of sequential use could be inferred. This was because the blinatumomab trial included patients treated in various lines of salvage, the comparator for second salvage would be standard of care chemotherapies, and blinatumomab had already been shown to be cost-effective against standard of care chemotherapies (and thus inotuzumab would be cost-effective by inference given it is recommended for listing on a cost-minimisation basis) .

- 7.16 The PBAC considered that uptake from therapies other than blinatumomab in first salvage was overestimated and should be reduced in the financial estimates. The PBAC also considered that the issues with rounding of scripts, averaging of costs and estimation of patient co-payments (as outlined in Paragraph 6.88) should be corrected.
- 7.17 The PBAC considered that the financial estimates would need to be updated to include the additional costs associated with sequential use of inotuzumab and blinatumomab. The PBAC considered these additional costs should include use in patients who require a second salvage due to either not proceeding to HSCT after first salvage or who relapse post-HSCT.
- 7.18 The PBAC considered that inotuzumab would need to join the existing RSA terms in place for blinatumomab, and that the associated financial caps could only be increased by the number of additional treatment courses expected with sequential use permitted. The PBAC considered that the number of treatment courses with blinatumomab or inotuzumab would increase by no more than 50% with sequential use permitted.
- 7.19 The PBAC considered that flow-on changes would be required to the existing blinatumomab restriction to allow use in patients with an ECOG status of 2, and to allow use in first and second salvage only. The PBAC considered that the number of patients likely to be impacted by these amendments was minimal, and the net overall effect (of these two amendments) would likely result in no change to net patient numbers.
- 7.20 The PBAC advised that inotuzumab is not suitable for prescribing by nurse practitioners.
- 7.21 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* inotuzumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.22 The PBAC recommended that inotuzumab should be exempt from the Early Supply Rule as it cannot currently be applied to Section 100 (Efficient Funding of Chemotherapy) program listings.

7.23 The PBAC noted that this submission was not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Induction

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
INOTUZUMAB OZOGAMICIN	3384 mcg	2	Besponsa®	Pfizer Australia P/L
Category/Program:	S100 – Efficient Funding of Chemotherapy (EFC)			
PBS indication:	Acute lymphoblastic leukaemia (ALL)			
Treatment phase:	Induction treatment			
Restriction:	Authority Required - In Writing			
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 Patient must have received intensive combination chemotherapy for initial treatment of ALL or subsequent salvage therapy, AND Patient must not have received more than 1 line of salvage therapy AND The condition must be Philadelphia chromosome negative, AND The condition must be CD22-positive, AND The condition must have more than 5% blasts in bone marrow, AND The treatment must not be more than 3 treatment cycles under this restriction in a lifetime.			
Prescriber instructions:	This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting. The authority application must be made in writing and must include: (1) a completed authority prescription form; (2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and (3) a signed patient acknowledgement; and (4) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage; and (5) a copy of the most recent bone marrow biopsy report of no more than one month old at the time of application. The treatment must not exceed 0.8mg per m ² for the first dose of a treatment cycle (Day 1), and 0.5mg per m ² for subsequent doses (Days 8 and 15) within a treatment cycle.			

Public Summary Document – November 2018 PBAC Meeting

Administrative advice	<p>Once a patient achieves complete remission or complete remission with partial haematological recovery, a new prescription must be written under the consolidation treatment phase.</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>A complete remission with partial haematological recovery is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a partial recovery of peripheral blood counts with platelets of greater than 50,000 per microliter, and absolute neutrophil count (ANC) of greater than 500 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>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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>
Cautions:	<p>Careful monitoring of patients is required due to risk of developing hepatotoxicity, including life-threatening hepatic veno-occlusive disease, and the increased risk of post-haematopoietic stem cell transplant non-relapse mortality observed in patients treated with inotuzumab.</p>

Continuing

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
INOTUZUMAB OZOGAMICIN				
1 mg vial powder for injection	2820 mcg	4	Besponsa®	Pfizer Australia P/L
Category/Program:	S100 – Efficient Funding of Chemotherapy (EFC)			
PBS indication:	Acute lymphoblastic leukaemia (ALL)			
Treatment phase:	Consolidation treatment			
Restriction:	Authority Required - Telephone			
Clinical criteria:	Patient must have previously received PBS-subsidised induction treatment with this drug for this condition, AND			

Public Summary Document – November 2018 PBAC Meeting

	<p>Patient must have achieved a complete remission; OR Patient must have achieved a complete remission with partial haematological recovery, AND The treatment must not be more than 5 treatment cycles under this restriction in a lifetime, AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.</p>
Prescriber instruction:	Treatment with this drug for this condition must not exceed 6 treatment cycles in a lifetime.
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>A complete remission with partial haematological recovery is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a partial recovery of peripheral blood counts with platelets of greater than 50,000 per microliter, and absolute neutrophil count (ANC) of greater than 500 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. 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 hepatotoxicity, including life-threatening hepatic veno-occlusive disease, and the increased risk of post-haematopoietic stem cell transplant non-relapse mortality observed in patients treated with inotuzumab.

Grandfathering

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
INOTUZUMAB OZOGAMICIN				
1 mg vial powder for injection	3384 mcg	1	Besponsa®	Pfizer Australia P/L
Category/Program:	S100 – Efficient Funding of Chemotherapy (EFC)			
PBS indication:	Acute lymphoblastic leukaemia (ALL)			
Treatment phase:	Grandfathering treatment			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Clinical criteria:	<p>Patient must have a documented history of relapsed or refractory B-precursor cell ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, AND Patient must have a documented history of receiving intensive combination chemotherapy for initial treatment of ALL or subsequent salvage therapy, AND Patient must not have received more than 2 lines of salvage therapy</p>			

Public Summary Document – November 2018 PBAC Meeting

	<p>AND The condition must be Philadelphia chromosome negative, AND The condition must be CD22 positive, AND Patient must have a documented history of more than 5% blasts in bone marrow prior to when the patient commenced inotuzumab AND Patient must have received treatment with this drug for this condition prior to [DATE OF PBS-LISTING] AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug</p>
<p>Prescriber Instructions:</p>	<p>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p> <p>Treatment with this drug for this condition must not exceed 6 treatment cycles in a lifetime.</p> <p>Patients who have received up to three treatment cycles as induction therapy with this drug for this condition prior to [DATE OF PBS LISTING] must have achieved a complete remission, or a complete remission with partial haematological recovery in order to continue with PBS-subsidised treatment with this drug.</p> <p>Patients who have received at least one treatment cycle as consolidation therapy with this drug for this condition prior to [DATE OF PBS LISTING] must have achieved a complete remission, or a complete remission with partial haematological recovery in order to continue with PBS-subsidised treatment with this drug.</p> <p>Patients who fail to demonstrate a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) after 3 cycles of PBS-subsidised treatment with this agent must cease PBS-subsidised treatment with this agent.</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 Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and (3) evidence that the condition is CD22-positive; and (4) date of most recent inotuzumab ozogamicin dose, if this was for induction or consolidation therapy, and how many treatment cycle(s) of PBS-subsidised inotuzumab ozogamicin will be required for completion of induction or consolidation therapy; and (5) date of latest chemotherapy prior to receiving non-PBS subsidised inotuzumab ozogamicin, and if it was the initial chemotherapy regimen or for salvage therapy and what line of salvage; and (6) a copy of bone marrow biopsy report prior to receiving non-PBS subsidised inotuzumab ozogamicin.
<p>Definitions</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>A complete remission with partial haematological recovery is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a partial recovery of peripheral blood</p>

	counts with platelets of greater than 50,000 per microliter, and absolute neutrophil count (ANC) of greater than 500 per microliter.
Administrative Advice:	<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). 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. 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>An increase in the maximum number of repeats of up to 2 will be allowed for completion of induction therapy.</p> <p>An increase in the maximum number of repeats of up to 4 will be allowed for completion of consolidation therapy.</p> <p>Special Pricing Arrangements apply.</p>
Cautions:	Careful monitoring of patients is required due to risk of developing hepatotoxicity, including life-threatening hepatic veno-occlusive disease, and the increased risk of post-haematopoietic stem cell transplant non-relapse mortality observed in patients treated with inotuzumab.

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

Pfizer welcomes the PBAC's recommendation to make Besponsa available for the treatment of Australian patients with this rare haematological cancer with a poor prognosis.