12.03 INOTUZUMAB OZOGAMICIN, Powder for IV infusion, 1 mg vial, Besponsa®, Pfizer Australia Pty Ltd

1 Purpose of Item

1.1 The correspondence requested an extension to the recommended listing of inotuzumab ozogamicin (herein referred to as 'inotuzumab') for the treatment of relapsed or refractory (R/R) Philadelphia chromosome negative (Ph-) CD22 positive B-cell precursor acute lymphocytic leukaemia (B-ALL) to include patients with R/R Philadelphia chromosome positive (Ph+) B-ALL.

2 Background

2.1 At its November 2018 meeting, the PBAC recommended the listing of inotuzumab for the treatment of R/R Ph- B-ALL on a cost-minimisation basis against blinatumomab.

2.2 At the November 2018 meeting, the clinician who presented at the sponsor hearing outlined that there may be important benefits of inotuzumab in patients with Ph+ disease, particularly given it was generally associated with a poorer prognosis (inotuzumab Public Summary Document (PSD), November 2018, paragraph 6.3). At the November 2018 meeting, 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" (inotuzumab PSD, November 2018, paragraph 7.3).

2.3 At the November 2018 meeting, 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 haematopoietic stem cell transplant (HSCT) or who progress after an HSCT (inotuzumab PSD, July 2018, paragraph 7.2). 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 (inotuzumab PSD, November 2018, paragraph 7.6).

2.4 To inform changes to the current RSA, the sponsor of inotuzumab provided information regarding the likely financial implications of expanding the intended PBS-restriction for inotuzumab to include patients with Ph+ R/R B-ALL (i.e. amending the listing so as not to restrict access based on Philadelphia chromosome status).

3 Current situation

3.1 TGA status: 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 ALL.

Restriction

3.2 The sponsor did not propose a revised restriction. Compared with an abridged version of the recommended induction restriction for Ph- patients, the PBAC's suggested deletions are in strikethrough.

Induction

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
INOTUZUMAB OZOGAMICIN				
1 mg vial powder for injection	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.

Estimated PBS usage & financial implications

3.3 The sponsor presented utilisation and financial estimates derived from estimates and assumptions from the November 2018 submission, which were based on the adult ALL population only. The sponsor noted that the frequency of Ph+ disease increases with age, and younger children (1-9 years) are reported to have a better prognosis. As such, the sponsor anticipated that the utilisation of inotuzumab for paediatric patients with Ph+ disease is likely to be minimal.

3.4 The key assumptions underpinning the estimates were:

- 25% of adult patients with R/R B-ALL have Ph+ disease.
- Based on advice from the sponsor's advisory board, the estimates assumed that TKIs will remain the standard of care first-line salvage treatment for patients with Ph+ disease, and thus the likely utilisation of inotuzumab will be in patients who are R/R to first-line salvage treatment with a TKI. Thus, the sponsor estimated that the likely utilisation of inotuzumab in the R/R Ph+ B-ALL population is expected to be patients in second-line salvage.
- The PBAC previously considered that no more than 50% of patients would require sequential (i.e. second-line salvage) use of blinatumomab or inotuzumab (inotuzumab PSD, July 2018, paragraph 6.85). To account for the poorer prognosis of Ph+ B-ALL patients, the sponsor assumed that [redacted]% of this patient population are likely to be R/R to first-line salvage treatment and eligible to proceed to second-line salvage treatment.
- Uptake of inotuzumab was estimated to be [redacted]% in Year 1 increasing to [redacted]% by Year 3. The sponsor stated this was conservative given the high clinical need.

3.5 The estimated number of patients and financial impact for the first six years of listing are presented in Table 1.

Table 1: Estimated utilisation and financial impacts for Philadelphia chromosome positive patients

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients with R/R B-ALL[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with Ph+ and CD22+ (25% x 95%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients R/R to 1st line salvage and eligible for 2nd line salvage ([redacted]%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab uptake (%)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Inotuzumab patients	[redacted][d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total 1 mg vials of inotuzumab [e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: B-ALL, B-cell precursor acute lymphoblastic leukaemia; DPMA, dispensed price for maximum amount; PBS, Pharmaceutical Benefits Scheme; Ph+, Philadelphia chromosome positive; RPBS, Repatriation Schedule of Pharmaceutical Benefits; R/R, relapsed/refractory

Notes:

[a] Estimated number of patients with R/R B-ALL after first line treatment from the November 2018 submission;

[b] Based on the estimate that 25% of the adult R/R B-ALL population have Ph+ disease from the November 2018 submission; and 95% have CD22-positive disease

[c] Based on assumption that [redacted]% of R/R Ph+ B-ALL patients require 2nd line salvage;

[d] Year 1 includes one grandfathered patient

[e] Based on a mean of 9.3 x 1 mg vials per course per patient from the INO-VATE trial presented in the November 2018 submission;

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million.

3.6 The total cost to the PBS/RPBS was estimated to be less than $10 million in Year 1 increasing to less than $10 million in Year 6. The sponsor stated that the estimated financial impact is conservative as cost-offsets from potential substitution for salvage chemotherapy regimens or further treatment with a TKI have not been accounted for, and the inotuzumab price has not been updated to reflect the confidential effective price required for the cost-minimisation against blinatumomab.

3.7 The PBAC recalled its previous advice that inotuzumab would need to join the existing Risk Sharing Arrangement (RSA) terms in place for blinatumomab (inotuzumab PSD, November 2018, paragraph 7.18). The PBAC noted that blinatumomab is also TGA-approved for patients with Ph+ disease.

4 PBAC Outcome

4.1 The PBAC deferred making a decision to extend the recommended listing of inotuzumab, which was for the treatment of relapsed or refractory (R/R) Ph- B-precursor acute lymphocytic leukaemia (B-ALL), to include patients with Ph+ disease. The PBAC deferred making a recommendation to enable further work on the restriction and financial estimates.

4.2 The PBAC considered that if it made a positive recommendation to extend the recommended listing of inotuzumab to include Ph+ patients, it would be appropriate to make the parallel amendment to the existing listing of blinatumomab. As such, the PBAC advised that it would welcome a proposal from the sponsor of blinatumomab for this patient group. The PBAC considered that the extension of both inotuzumab and blinatumomab listings should be progressed in parallel.

4.3 The PBAC reaffirmed there is a high clinical need in patients with Ph+ disease (R/R B-ALL) particularly given it is generally associated with a poorer prognosis than Ph- disease.

4.4 The PBAC recalled that the INO-VATE ALL trial, which was the key trial of inotuzumab, presented in the November 2018 PBAC submission, included patients with Ph+ disease (15% of patients in the INO-VATE ALL trial were Ph+) and that the rate of complete remission in these patients was similar to the ITT population (78.6% versus 80.7%, respectively). Although the PBAC noted that *post hoc* subgroup analyses of the INO-VATE ALL trial found that, in patients with Ph+ disease, the rate of complete remission (or complete remission with incomplete hematologic recovery) with inotuzumab versus standard care was not statistically significantly different (34.1% increase (95% confidence interval (CI): -1.8%, 70.1%), it noted this analysis was based on small patient numbers. As such, the PBAC considered that overall, the treatment effect was unlikely to differ significantly based on Philadelphia chromosome status.

4.5 The PBAC was satisfied that by inference, inotuzumab would be sufficiently cost-effective in Ph+ disease.

4.6 The PBAC noted that the financial estimates assumed that TKIs would likely remain

the standard of care first-line salvage treatment in the Ph+ population, and thus inotuzumab would likely be used in second-line salvage in this population. However, the PBAC considered that for a small proportion of patients it may be clinically appropriate for inotuzumab to be used in combination with a TKI.

4.7 The PBAC noted that flow-on changes may be required to the TKI restrictions to allow use in combination with inotuzumab (e.g. the current listings for ponatinib and dasatinib in relapsed/refractory ALL state that the treatment must be the sole PBS-subsidised therapy for this condition).

4.8 The PBAC considered that, should both inotuzumab and blinatumomab be made available in patients with Ph+ disease, the overall uptake rates would be higher, and the market share of each agent would need to be estimated. The PBAC advised that it may also be appropriate to revise the financial estimates to account for use in first-line salvage, although this use is expected to be small.

4.9 The PBAC noted that the financial impact was likely to be small relative to the Ph- patient population given the small number of patients with this condition. The PBAC considered that the financial estimates were likely to be overestimated, as cost offsets due to substitution for salvage chemotherapy were not included.

4.10 The PBAC considered that the RSA would need to be updated to include patients with Ph+ R/R B-ALL disease, and that the associated financial caps could only be increased by the number of additional treatment courses expected with the extension of the existing listing to Ph+ disease.

Outcome:
Deferred

Addendum to the March 2019 PBAC Minutes:

7.02a INOTUZUMAB OZOGAMICIN, Powder for IV infusion, 1 mg vial, Besponsa®, Pfizer Australia Pty Ltd

4.11 The PBAC recommended extending the listings of inotuzumab and blinatumomab to include patients with Ph+ disease on the basis that it considered inotuzumab and blinatumomab would be sufficiently effective and cost-effective in patients with Ph+ disease. The PBAC considered the financial impact of amending the restrictions for both drugs would be relatively small compared to the Ph- population (see 7.02b blinatumomab PSD, May 2019).

4.12 At its meeting on 3 May 2019, the PBAC considered information provided by the sponsor of blinatumomab in relation to extending the existing listing of blinatumomab for the treatment of relapsed or refractory (R/R) Philadelphia chromosome negative (Ph-) B-cell precursor acute lymphocytic leukaemia (B-ALL) to include patients with R/R Philadelphia chromosome positive (Ph+) B-ALL (refer to 7.02b blinatumomab PSD, May 2019). The PBAC considered that this additional information had enabled an assessment of the total financial impact of amending the restrictions for both drugs, and was sufficient to address its previous concern about quantifying the total financial impact of this amendment. The PBAC noted that the estimates provided by the blinatumomab sponsor appropriately included both blinatumomab and inotuzumab, and also appropriately included use in first-line salvage.

4.13 The PBAC considered that it may be clinically appropriate for blinatumomab or inotuzumab to be used in combination with a TKI.

4.14 Given TKIs are standard care in previously untreated Ph+ B-ALL (initial first-line treatment), the PBAC considered it would be appropriate to limit use of blinatumomab and inotuzumab to Ph+ patients previously treated with a TKI.

4.15 The PBAC considered that the restrictions for inotuzumab and blinatumomab should align where possible.

4.16 The PBAC noted the financial impact of extending the current listings of blinatumomab and inotuzumab to Ph+ R/R B-ALL patients was likely to be small relative to the Ph- patient population given the small number of patients. The PBAC considered that the underlying assumptions used by the sponsor of blinatumomab to estimate the utilisation of both blinatumomab and inotuzumab in Ph+ patients (in first- and second-line salvage) were reasonable noting that the estimates generally aligned with those provided for inotuzumab in second-line salvage in the March 2019 meeting (Refer to Section 4, 7.02b blinatumomab PSD, May 2019).

4.17 The PBAC considered that the existing RSAs for blinatumomab and inotuzumab would

need to be updated to include the estimated cost of treatment for new patients with Ph+ disease. The PBAC noted that any increase to the associated financial caps should only be based on the number of additional treatment courses expected with the extension of the existing listing to patients with Ph+ disease. The PBAC considered that the financial estimates should account for no more than [redacted]% of patients receiving sequential therapy with these agents consistent with its previous advice.

4.18 The PBAC noted that flow-on changes would be required to the existing TKI restrictions to allow use in combination with blinatumomab or inotuzumab.

Outcome:
Recommended

5 Recommended listing

5.1 Amend existing listings:

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
INOTUZUMAB OZOGAMICIN				
1 mg injection, 1 vial	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~~ *Patient must have previously received a tyrosine kinase inhibitor if the condition is Philadelphia chromosome positive,* 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 administered to an in-patient in a public hospital setting. The authority application must be made in writing and must include: (1) two completed authority prescription forms; (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 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 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. Treatment with this drug for this condition must not exceed 6 treatment cycles in a lifetime.

Administrative advice	Patients are eligible to receive a loading dose for the first dose of a treatment cycle while receiving induction treatment. Two prescriptions are required, the first prescription for the loading dose at a dose no higher than 0.8mg per m2, and the second prescription for two doses at a dose no higher than 0.5mg per m2. Both prescriptions must be submitted with the initial application. Once a patient achieves complete remission or complete remission with partial haematological recovery, a new prescription must be written under the consolidation treatment phase. 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. 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. 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. 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
Cautions:	Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.

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~~ *Patient must have previously received a tyrosine kinase inhibitor if the condition is Philadelphia chromosome positive,* 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 administered to an in-patient in a public hospital setting. The authority application must be made in writing and must include: (1) two completed authority prescription forms; (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 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 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. Treatment with this drug for this condition must not exceed 6 treatment cycles in a lifetime.
Administrative advice	Patients are eligible to receive a loading dose for the first dose of a treatment cycle while receiving induction treatment. Two prescriptions are required, the first prescription for the loading dose at a dose no higher than 0.8mg per m2, and the second prescription for two doses at a dose no higher than 0.5mg per m2. Both prescriptions must be submitted with the initial application. Once a patient achieves complete remission or complete remission with partial haematological recovery, a new prescription must be written under the consolidation treatment phase.

	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. 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. 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. 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 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.
Cautions:	Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.

6 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.

7 Sponsor's Comment

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