Technology Guidance

Blinatumomab

for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended blinatumomab powder for infusion 35 mcg/vial for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia (r/r B-ALL) for:

- ✓ up to a maximum of two cycles for induction in a lifetime; and
- ✓ up to three additional cycles for consolidation in a lifetime in patients who achieve a complete response after induction.

Patients with Philadelphia chromosome positive disease must have previously received a tyrosine kinase inhibitor before receiving blinatumomab.

Patients must not have received blinatumomab previously for the treatment of minimal residual disease (MRD)-positive B-ALL OR patients must have had a relapse-free period of at least six months following completion of treatment with blinatumomab for MRD.

Complete response is defined as a patient who:

- has 5% or less bone marrow blasts; and
- has no evidence of disease; and
- has platelet count of more than 50,000 per microlitre; and
- has absolute neutrophil count of more than 500 per microlitre.

Subsidy status

Blinatumomab powder for infusion 35mcg/vial is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

Updated: 4 January 2022

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of blinatumomab for treating r/r B-ALL. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical evidence and ACE's in-house economic evaluation for blinatumomab were considered in line with the registered indication. The use of blinatumomab for treating patients with B-ALL who are in complete remission was outside the scope of evaluation.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. The Committee noted that approximately 12 patients are diagnosed with r/r B-ALL each year in Singapore. In local clinical practice, treatment strategies are guided by the presence of the Philadelphia (Ph) chromosome, which is found in 5% of children and 30% of adults with ALL, and is associated with poor prognosis. Blinatumomab monotherapy is the preferred first-line therapeutic option for Ph-negative r/r B-ALL, owing to its favourable efficacy and tolerability profile compared to the most commonly used chemotherapy regimen, FLAG-IDA (fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor). For patients with Ph-positive disease, blinatumomab may be used if they are intolerant of, or refractory to, tyrosine kinase inhibitors.

2.2. A treatment course consists of up to two cycles of blinatumomab for induction followed by three additional cycles for consolidation. The primary goal of treatment is to achieve complete remission or sufficient cytoreduction to enable allogeneic hematopoietic stem cell transplantation, which may offer a chance of cure in a small, highly selected group of patients. The Committee noted that the high cost of blinatumomab is currently a barrier to prescribing, and agreed that there was a high clinical need to consider it for subsidy to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

3.1. One phase III randomised controlled trial (TOWER) was identified which compared blinatumomab monotherapy with chemotherapy in adults with Ph-negative r/r B-ALL. The Committee considered that although the comparator in the study comprised four different chemotherapy regimens, FLAG-IDA was most commonly used, therefore, results were likely to be generalisable to the local context. The Committee noted that blinatumomab led to statistically longer median overall survival of 3.7 months, 29% lower risk of death and clinically significant improvements in health-related quality of life, with more patients achieving complete remission compared to chemotherapy (19.3% more).

3.2. The Committee acknowledged that blinatumomab had a more favourable safety profile than chemotherapy. However, cases of cytokine release syndrome reported in the pivotal study were unique to blinatumomab use (5% vs 0% with chemotherapy), although none led to treatment discontinuation.

3.3. The Committee further reviewed a phase I/II single-arm study in children with r/r B-ALL and a phase II single-arm trial in adults with Ph-positive r/r B-ALL. They noted that the efficacy and safety results in these studies were comparable to results in the blinatumomab arm of the pivotal TOWER study. No additional studies were identified.

Cost effectiveness

4.1. The Committee considered results from ACE's cost-effectiveness analysis which compared blinatumomab with FLAG-IDA in patients with r/r B-ALL. For adults who received the first five cycles for induction and consolidation, blinatumomab was associated with a base-case incremental cost-effectiveness ratio (ICER) of SG$15,000 to <SG$45,000 per QALY gained compared with FLAG-IDA. A scenario analysis which included an additional four cycles for maintenance treatment in <10% of patients led to a substantial increase in the ICER, but it still fell within the range of SG$15,000 to <SG$45,000 per QALY gained. Scenario analyses of blinatumomab for treating paediatric patients resulted in a more favourable ICER of <SG$15,000 per QALY gained.

4.2. The Committee observed that the cost-effectiveness of blinatumomab was uncertain as the ICER increased when the maintenance cycles were included, despite the low proportion of patients involved (<10%). They noted that most overseas reference HTA agencies (e.g. NICE (UK) and PBAC (Australia)) only reimburse the first five cycles of treatment in a lifetime due to cost-effectiveness concerns. Taking these factors into consideration, the Committee concluded that blinatumomab was a cost-effective option for treating patients with r/r B-ALL for up to five treatment cycles in a lifetime only.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact was estimated to be between SG$500,000 to less than SG$1 million in the first year of listing blinatumomab on the MAF.

Additional considerations

6.1. The Committee acknowledged that, contingent on subsidy listing, the manufacturer had agreed to implement an improved patient assistance programme (PAP) for eligible patients with r/r B-ALL who require blinatumomab, which would provide further savings to patients in addition to MAF subsidy.

Recommendations

7.1. Based on available evidence, the Committee recommended blinatumomab powder for infusion 35 mcg/vial be listed on the MAF for treating r/r B-ALL for up to five cycles in a lifetime, in line with specific clinical criteria, and provided that the PAP proposed by the manufacturer is implemented for all eligible patients, in view of its favourable clinical and cost-effectiveness, and the high clinical need for this treatment to ensure appropriate patient care.

VERSION HISTORY

Guidance on blinatumomab for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

Date of Publication	1 September 2020

2. **Clinical criteria updated following MAF listing of blinatumomab for MRD-positive B-ALL.**

Date of Publication	4 January 2022