Technology Guidance

Review of cancer drugs for

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;
- ✓ Dasatinib 20 mg, 50 mg and 70 mg tablets;
- ✓ Ponatinib 15 mg tablets; and
- ✓ Inotuzumab ozogamicin 1 mg powder for concentrate for solution for infusion

for treating acute lymphoblastic leukaemia (ALL) in line with specific clinical criteria.

Subsidy status

Blinatumomab powder for infusion 35 mcg/vial is recommended for inclusion on the Medication Assistance Fund (MAF) with effect from 4 January 2022[a] for treating patients with B-precursor ALL in first or subsequent complete remission with minimal residual disease (MRD) for:

- up to a maximum of one cycle for induction in a lifetime; and
- up to three additional cycles for consolidation in a lifetime.

Complete remission is defined as a patient who:

a) has 5% or less bone marrow blasts; and
b) has no evidence of disease; and
c) has a full recovery of peripheral blood counts with platelet count of more than 100,000 per microlitre; and
d) has absolute neutrophil count of more than 1,000 per microlitre.

Dasatinib 20 mg, 50 mg and 70 mg tablets are recommended for inclusion on MAF with effect from 1 September 2022 for treating patients with:

- newly diagnosed Philadelphia chromosome positive ALL (Ph+ALL) in combination with chemotherapy; or
- Ph+ALL with resistance or intolerance to prior treatment with imatinib.

Updated: 13 September 2024

Ponatinib 15 mg tablet is recommended for inclusion on MAF with effect from 1 September 2022 for treating patients:

- with Ph+ALL who are resistant to dasatinib;
- who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or
- who have the T315I mutation.

Inotuzumab ozogamicin 1 mg powder for concentrate for solution for infusion is recommended for inclusion on MAF with effect from 1 April 2022 for treating patients with relapsed or refractory CD22 positive B-precursor ALL for:

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

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

Complete response is defined as a patient who:

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

Clinical indications, subsidy class and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.

[a] revised clinical indication with effect from 1 Nov 2024.

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, dasatinib, ponatinib and inotuzumab ozogamicin ("inotuzumab") for treating acute lymphoblastic leukaemia (ALL). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE in ascertaining the clinical value of the drugs under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.

1.2 The use of clofarabine for treating children with relapsed or refractory ALL was outside the scope of the evaluation following advice from local clinical experts and ODS members who advised that there was no clinical need to consider this treatment for subsidy. The 45 mg strength of ponatinib was excluded from evaluation as it is not commercially available in Singapore.

1.3 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.

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

Clinical need

2.1 The Committee noted that ALL comprises less than 1% of adult cancers but represents the most common childhood malignancy, accounting for approximately 25% of cancers and 80% of all leukaemia cases in children. Hence there is a high clinical need to consider treatments for subsidy to improve treatment affordability and ensure appropriate patient care.

2.2 <u>Treatment of Philadelphia chromosome positive ALL</u>
The Committee acknowledged that tyrosine kinase inhibitors (TKIs) are the standard of care for patients with Philadelphia chromosome positive ALL (Ph+ALL). Locally,

newly diagnosed patients are treated with either imatinib (listed on the MOH SDL [1]) or dasatinib in combination with chemotherapy. If drug intolerance occurs, patients may switch between either agent. Patients who develop resistance to imatinib may then receive dasatinib, or ponatinib if they are adults whose ALL has the T315I mutation. Adults who develop resistance to dasatinib may receive ponatinib as a last line TKI. The Committee acknowledged that local clinical practice is in line with international clinical practice guidelines.

2.3 Treatment of B-precursor ALL in complete remission with MRD

Local clinical practice for children varies according to public healthcare institutions and those with minimum residual disease (MRD)-positive precursor B-ALL may receive blinatumomab as a bridge to haematopoietic stem cell transplant (HSCT). Adults with Philadelphia chromosome negative disease may be treated with blinatumomab while those with Ph+ disease tend to continue treatment with a TKI until MRD-negative status is achieved before proceeding with HSCT.

2.4 Treatment of relapsed or refractory B-precursor ALL

In local practice, both blinatumomab (anti-CD19, listed on the MAF [2]) and inotuzumab (anti-CD22) are used to treat relapsed or refractory B-precursor ALL to achieve complete remission and facilitate HSCT, in line with international clinical practice guidelines.

Clinical effectiveness and safety

3.1 Treatment of Ph+ ALL

Dasatinib

The Committee reviewed two randomised controlled trials (RCTs) and five single-arm studies and considered that treatment regimens incorporating dasatinib resulted in high rates of initial complete response in newly diagnosed patients or those who developed resistance or intolerance to prior treatment with imatinib. The studies did not report additional serious adverse events related to dasatinib use.

3.2 The Committee noted a head-to-head trial (CCCG-ALL-2015) which showed similar rate of initial complete response between dasatinib and imatinib, while overall survival (OS) results were immature. The Committee heard that there were differences between dosages of TKIs used in studies versus local practice, and further considered that dasatinib may be a better treatment option for some patients, given its penetration into the central nervous system (CNS) and poorer outcomes associated with CNS recurrence.

3.3 **Ponatinib**

The Committee reviewed the available clinical evidence (PACE, single-arm study) that investigated ponatinib in adults with Ph+ALL who are resistant or intolerant to dasatinib

[1] ACE Technology guidance for imatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia.
[2] ACE Technology guidance for blinatumomab for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia.

or who developed the T315I mutation after any TKI therapy. In the absence of comparative trials with chemotherapy or other TKIs, the Committee considered ponatinib to be an effective treatment for these patients but noted that the magnitude of benefit was uncertain. Overall ponatinib was generally well tolerated but was associated with cardiovascular adverse events such as arterial occlusion, venous thromboembolism and heart failure.

3.4 Treatment of B-precursor ALL in complete remission with MRD

The Committee reviewed two single-arm studies and acknowledged results from indirect evidence considered by PBAC (Australia) which suggested that blinatumomab improved relapse-free survival with no OS gain when compared with standard of care chemotherapy. The Committee considered blinatumomab was effective in eliminating MRD and led to durable relapse-free survival. The most common grade 3 or 4 adverse event associated with blinatumomab was neutropoenia followed by pyrexia and leucopoenia.

3.5 Treatment of relapsed or refractory CD22 positive B-precursor ALL

The Committee reviewed one phase III RCT (INO-VATE ALL) comparing inotuzumab with standard of care chemotherapy in adults with relapsed or refractory CD22-positive B-precursor ALL eligible for first or second salvage therapy. Results showed that inotuzumab significantly extended progression-free survival (PFS), but not OS, compared to chemotherapy. The incidences of serious adverse events were comparable between the two treatment arms, however inotuzumab was associated with higher rates of veno-occlusive liver disease compared with chemotherapy.

3.6 The Committee also acknowledged results from indirect evidence considered by PBAC which suggested that inotuzumab has comparable clinical efficacy and different but non-inferior safety profiles compared with blinatumomab.

Cost-effectiveness

4.1 The manufacturers of all drugs under evaluation were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration.

4.2 Treatment of Ph+ ALL

Dasatinib and ponatinib

In the absence of a local cost-effectiveness evaluation, the Committee reviewed results of evaluations from overseas HTA agencies and agreed that they were likely to be generalisable to the local context. The Committee noted that, at the local proposed prices, the cost of treatment with dasatinib was higher than that of generic imatinib, and the cost of treatment with ponatinib was higher than that of dasatinib. Nonetheless, the prices of dasatinib and ponatinib were aligned to prices in overseas reference jurisdictions.

4.3 Treatment of B-precursor ALL in complete remission with MRD

The Committee reviewed results from overseas HTA agencies and agreed that the ICERs for blinatumomab compared with chemotherapy were likely to be acceptable in

local context at the proposed price, which was comparable with overseas reference jurisdictions.

4.4 Treatment of relapsed or refractory CD22 positive B-precursor ALL
The Committee noted that the at the local proposed price, the average treatment cost for inotuzumab (up to 6 cycles) was comparable with blinatumomab (up to 5 cycles), and agreed that inotuzumab was cost-effective on a cost-minimisation basis versus blinatumomab.

Estimated annual technology cost

5.1 Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact in the first year of listing each drug on the MAF was estimated to be less than S$1 million each.

Additional considerations

6.1 The Committee acknowledged that, contingent on subsidy listing, the manufacturer of blinatumomab had agreed to extend the current patient assistance programme (PAP) for blinatumomab to eligible patients with MRD-positive B-precursor ALL, which would improve treatment affordability in addition to MAF financial assistance.

Recommendations

7.1 Treatment of Ph+ ALL
Based on available evidence, the Committee recommended dasatinib 20 mg, 50 mg and 70 mg tablets and ponatinib 15 mg tablets be listed on the MAF for treating Ph+ ALL, in view of the high clinical need and acceptable clinical and cost-effectiveness.

7.2 Treatment of B-precursor ALL in complete remission with MRD
The Committee recommended blinatumomab powder for infusion 35 mcg/vial be listed on the MAF for treating MRD-positive B-precursor ALL, in view of the high clinical need and acceptable clinical and cost-effectiveness with the PAP proposed by the manufacturer.

7.3 Treatment of relapsed or refractory CD22 positive B-precursor ALL
The Committee recommended inotuzumab ozogamicin 1 mg powder for concentrate for solution for infusion be listed on MAF for treating adults with relapsed or refractory CD22 positive B-precursor ALL, in view of favourable clinical and cost-effectiveness.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Treatment of Philadelphia chromosome positive ALL			
Dasatinib 20 mg, 50 mg and 70 mg tablets	Treatment of newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia in combination with chemotherapy. Treatment of patients with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior treatment with imatinib.	MAF (1 Sep 2022)	$1200 (1 Sep 2022)
Ponatinib 15 mg tablet	Treatment of patients with Philadelphia chromosome positive acute lymphoblastic leukaemia who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.	MAF (1 Sep 2022)	$1200 (1 Sep 2022)
Treatment of B-precursor ALL in complete remission with MRD			
Blinatumomab powder for infusion 35 mcg/vial	Treatment of B-precursor acute lymphoblastic leukaemia in first or subsequent complete remission with minimal residual disease (MRD) for: – up to a maximum of one cycle for induction in a lifetime; and – up to three additional cycles for consolidation in a lifetime.[a] Complete remission is defined as a patient who: a) has 5% or less bone marrow blasts; and b) has no evidence of disease; and c) has a full recovery of peripheral blood counts with platelet count of more than 100,000 per microlitre; and d) has absolute neutrophil count of more than 1,000 per microlitre	MAF (4 Jan 2022)	$9600 (1 Sep 2022)

Treatment of relapsed or refractory CD22 positive B-precursor ALL			
Inotuzumab ozogamicin 1 mg powder for concentrate for solution for infusion	Treatment of patients with relapsed or refractory CD22-positive B-precursor acute lymphoblastic leukemia (ALL) for: – up to a maximum of three 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 inotuzumab. Complete response is defined as a patient who: a) has 5% or less bone marrow blasts; and b) has no evidence of disease; and c) has platelet count of more than 50,000 per microlitre; and d) has absolute neutrophil count of more than 500 per microlitre.	MAF (1 Apr 2022)	$9600 (1 Sep 2022)

Abbreviations: ALL, acute lymphoblastic leukaemia; MAF, Medication Assistance Fund; MRD, minimal residual disease; MSHL, MediShield Life

[a] revised clinical indication with effect from 1 Nov 2024.

VERSION HISTORY

Update of Review of cancer drugs for 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 4 Jan 2022

2. **Guidance updated with the following changes:**
   - revised clinical indication for blinatumomab

   Date of Publication 13 Sep 2024

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about