ACE agency for care effectiveness

Technology Guidance

[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 2 JANUARY 2024.]

Review of cancer drugs

for chronic lymphocytic leukaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Acalabrutinib 100 mg capsule;
- ✓ Obinutuzumab 1000 mg/40 mL concentrate for solution for infusion; and
- ✓ Venetoclax 10 mg, 50 mg, and 100 mg tablets

for treating chronic lymphocytic leukaemia (CLL) in line with specific clinical criteria.

Subsidy status

Acalabrutinib 100 mg capsule is recommended for inclusion on the Medication Assistance Fund (MAF) as monotherapy:

- for previously untreated CLL or small lymphocytic lymphoma (SLL) in patients who are unsuitable for fludarabine-based therapy; and
- for relapsed or refractory CLL or SLL in patients who have received at least one prior therapy.

Venetoclax 10 mg, 50 mg and 100 mg tablets are recommended for inclusion on the MAF

- in combination with obinutuzumab or as monotherapy after completion of six cycles of obinutuzumab for previously untreated CLL in patients who are unsuitable for fludarabine-based therapy; and
- in combination with rituximab biosimilar (subsidised brand) or as monotherapy after completion of six cycles of rituximab for treating relapsed or refractory CLL in patients who have received at least one prior therapy.

All drugs should be used according to the treatment regimens outlined in the Annex.
MAF assistance will be implemented from 1 September 2022.

MAF assistance **does not** apply to any formulations or strengths of ibrutinib, obinutuzumab when used with chlorambucil, acalabrutinib when used with obinutuzumab, or venetoclax when used with unsubsidised brands of rituximab for treating CLL.

Published: 1 August 2023

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

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 Bruton's tyrosine kinase (BTK) inhibitors (acalabrutinib and ibrutinib), obinutuzumab and venetoclax for treating chronic lymphocytic leukaemia (CLL). 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 were considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain 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 ibrutinib in combination with bendamustine and rituximab; and venetoclax monotherapy for relapsed or refractory CLL were outside the scope of the evaluation following advice from local clinical experts and ODS members that there was no clinical need for these indications to be evaluated.

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 acknowledged that CLL and small lymphocytic lymphoma (SLL) (both often referred to as CLL) are indolent B-cell malignancies primarily affecting older adults, with approximately 30 to 40 new cases diagnosed each year in Singapore. The median survival for patients with CLL ranges from 6.5 years to more than 10 years depending on the stage of the disease and other genetic prognostic factors. While most patients with asymptomatic, early stage CLL or SLL do not require treatment, local clinical experts confirmed that 10 to 15 patients will need to commence treatment each year for advanced, symptomatic, or active disease.

2.2. The Committee heard from the local clinical experts that patients with a chromosome 17p deletion (del 17p), TP53 mutation and/or unmutated immunoglobulin heavy chain variable (IGHV) often have a worse prognosis and are usually resistant to standard chemoimmunotherapy regimens (e.g., fludarabine, cyclophosphamide plus rituximab (FCR), bendamustine plus rituximab or chlorambucil plus rituximab). However, targeted therapies such as BTK inhibitors (acalabrutinib and ibrutinib) and B-cell lymphoma 2 (BCL2) inhibitors (venetoclax) can be clinically effective in these patients; therefore, there was an unmet clinical need to consider them for subsidy to ensure appropriate patient care.

2.3. Previously untreated CLL

For patients with a del(17p) or TP53 mutation

The Committee heard that BTK inhibitors were routinely used in local practice for patients with a del(17p) or TP53 mutation, while venetoclax (for up to 12 months) plus obinutuzumab (up to 6 cycles) was usually reserved for patients who prefer a fixed treatment duration.

2.4. **For fit patients without a del(17p) or TP53 mutation who are <65 years**

The Committee heard that FCR was the standard of care in local practice for fit patients with previously untreated CLL without del(17p) or TP53 mutations in line with international clinical practice guidelines, and all drugs in the FCR regimen were already listed on SDL. However, BTK inhibitors were increasingly being prescribed for this patient subgroup.

2.5. **For patients without a del(17p) or TP53 mutation who are ≥65 years or <65 years with comorbidities**

The Committee heard that BTK inhibitors were routinely used in local practice for older patients (≥65 years), or for patients <65 years with comorbidities without a del(17p) or TP53 mutation. Venetoclax (for up to 12 months) plus obinutuzumab (up to 6 cycles) was also used if patients prefer a fixed treatment duration. Local clinical experts confirmed that chlorambucil plus obinutuzumab was seldom used for these patients given the availability of more effective treatments. The Committee considered that there was an unmet clinical need to subsidise at least one treatment to improve affordability for patients who are unable to receive FCR.

2.6. Relapsed or refractory CLL

The Committee noted that approximately 10 patients with CLL will experience disease progression each year despite initial therapy and will require BTK inhibitors or venetoclax (for up to 24 months) plus rituximab biosimilar (up to 6 cycles) to manage their condition. The Committee acknowledged that there was an unmet clinical need to subsidise at least one treatment option for patients with relapsed or refractory CLL, given that none of the treatments were included in the MOH List of Subsidised Drugs at the time of evaluation, representing a therapeutic gap.

Clinical effectiveness and safety

3.1. Previously untreated CLL

For fit patients without a del(17p) or TP53 mutation who are <65 years

The Committee reviewed the available clinical evidence for ibrutinib plus rituximab (E1912 study) for fit patients with previously untreated CLL without a genetic mutation. While the results suggested that ibrutinib plus rituximab was more effective than FCR, median progression-free survival (PFS) and overall survival (OS) were not reached in both treatment arms.

3.2. In terms of safety, the Committee noted that the incidences of Grade ≥3 adverse events (AEs) were similar between treatment arms. While FCR was associated with more myelosuppression, ibrutinib plus rituximab was associated with more cardiovascular and bleeding AEs.

3.3. **For patients with a del(17p) or TP53 mutation or who are ≥65 years or <65 years with comorbidities**

The Committee reviewed the available clinical evidence for acalabrutinib (ELEVATE-TN), ibrutinib (RESONATE-2) and venetoclax plus obinutuzumab (CLL 14) for previously untreated patients with CLL who were at least 65 years old, or less than 65 years with comorbidities. The study treatment in all three trials demonstrated significant PFS improvement compared to chlorambucil (RESONATE-2) or chlorambucil plus obinutuzumab (ELEVATE-TN and CLL 14). Efficacy was maintained in patient subgroups with del(17p) or TP53 mutations. In terms of OS, the Committee acknowledged that results from RESONATE-2 showed that ibrutinib was superior to chlorambucil; however, OS data for ELEVATE-TN and CLL 14 remained immature. The Committee noted that the trials for BTK inhibitors in combination with obinutuzumab (ELEVATE-TN [acalabrutinib] and iLLUMINATE [ibrutinib]) were not designed to compare the efficacy and safety of the combination regimens versus BTK inhibitor monotherapy and therefore, the benefit of adding obinutuzumab to BTK inhibitor monotherapy for previously untreated CLL remained uncertain.

3.4. In terms of safety, the Committee noted that acalabrutinib and ibrutinib were associated with more cardiovascular AEs (e.g., atrial fibrillation and bleeding) while venetoclax plus obinutuzumab was associated with more gastrointestinal AEs (e.g., diarrhoea) and an increased risk of tumour lysis syndrome.

3.5. In view of a lack of head-to-head trials comparing the treatments with each other, the Committee concluded that there was no evidence to support the superiority of venetoclax-based treatment or either BTK inhibitor for previously untreated CLL.

3.6. Relapsed or refractory CLL

The Committee reviewed the available clinical evidence for acalabrutinib (ASCEND),

ibrutinib (RESONATE) and venetoclax plus rituximab (MURANO) in patients with relapsed or refractory CLL, and noted that the study treatment in all three trials demonstrated significant PFS improvements compared to ofatumumab (RESONATE), idelalisib plus rituximab or bendamustine plus rituximab (ASCEND) and bendamustine plus rituximab (MURANO). Efficacy was also maintained in high-risk subgroups. While MURANO was the only trial to show improved OS, the Committee acknowledged that a large proportion of patients in the ASCEND (51%) and RESONATE (68%) trials crossed over from the comparator arms. The Committee also noted that ofatumumab is not routinely used in local practice, therefore, the RESONATE trial was likely to have limited generalisability to the Singapore context.

3.7. The Committee acknowledged that indirect comparisons submitted to overseas HTA agencies reported no meaningful differences in efficacy and safety between venetoclax plus rituximab, ibrutinib and acalabrutinib; however, the treatments had different toxicity profiles.

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. Venetoclax for CLL

The Committee noted that most overseas reference HTA agencies had recommended listing venetoclax in combination with obinutuzumab for previously untreated CLL, or in combination with rituximab for relapsed or refractory CLL. The Committee considered that these treatments were given for a fixed duration and concluded that an MAF listing was appropriate in view of acceptable cost-effectiveness at the prices and price volume agreements (PVAs) proposed by the manufacturers.

4.3. BTK inhibitors for CLL

The Committee acknowledged that most overseas reference HTA agencies had recommended listing BTK inhibitors (ibrutinib and acalabrutinib) for previously untreated and relapsed or refractory CLL conditional on confidential price reductions or risk sharing arrangements agreed with the manufacturers. The Committee noted that an agreement to sign a PVA was not reached with the manufacturer of ibrutinib to manage budget uncertainty associated with a potentially long and unknown treatment duration. The manufacturer of acalabrutinib however, did propose a PVA which the Committee considered was acceptable to manage the high and uncertain budget impact. In view of the clinical comparability of BTK inhibitors for treating CLL, the Committee agreed that acalabrutinib was likely to be more cost-effective than ibrutinib based on the manufacturers' pricing proposals.

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 MAF for treating CLL was estimated to be:

- Acalabrutinib: between SG$1 million to less than SG$3 million;
- Obinutuzumab: less than SG$1 million; and
- Venetoclax: less than SG$1 million.

Additional considerations

6.1. The Committee acknowledged that the manufacturers of acalabrutinib and venetoclax agreed to implement patient assistance programs (PAPs) in the public healthcare institutions, contingent on subsidy listing, which would provide further savings to eligible patients in addition to MAF assistance.

Recommendations

7.1. In view of the clinical need to subsidise a BTK inhibitor to ensure appropriate patient care, the Committee recommended acalabrutinib 100 mg capsule be listed on the MAF for patients with previously untreated CLL or SLL who are unsuitable for fludarabine-based therapy; and for patients with relapsed or refractory CLL or SLL who have received at least one prior therapy, contingent on a PVA with the manufacturer to improve cost-effectiveness and ensure budget certainty.

7.2. Based on available evidence, the Committee recommended venetoclax 10 mg, 50 mg and 100 mg tablets be listed on the MAF in combination with obinutuzumab 1000 mg/40 mL concentrate for solution for infusion (or as monotherapy after six cycles of obinutuzumab have been completed) for treating patients with previously untreated CLL who are unsuitable for fludarabine-based therapy, in view of acceptable clinical and cost-effectiveness at the proposed prices and PVAs agreed with the manufacturers.

7.3. The Committee also recommended venetoclax in combination with rituximab biosimilar (or as monotherapy after six cycles of rituximab have been completed) be listed on the MAF for treating patients with relapsed or refractory CLL who have received at least one prior therapy in view of acceptable clinical and cost-effectiveness at proposed prices and PVAs agreed with the manufacturer.

7.4. The Committee recommended not listing obinutuzumab in combination with chlorambucil on the MAF for patients with previously untreated CLL, given the low

clinical need for this treatment in local practice. The Committee also recommended not listing ibrutinib (monotherapy and combination therapy for previously untreated or relapsed or refractory CLL); acalabrutinib in combination with obinutuzumab (for previously untreated CLL) or venetoclax in combination with unsubsidised brands of rituximab on the MAF in view of unfavourable cost-effectiveness at the prices proposed by the manufacturers.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy Class (implementation date)	MediShield Life claim limit per month (implementation date)
Previously untreated chronic lymphocytic leukaemia (CLL)			
Acalabrutinib 100 mg capsule	As monotherapy for previously untreated CLL/SLL in patients who are unsuitable for fludarabine-based therapy.	MAF (1 Sep 2022)	$2000 (1 Sep 2022)
Acalabrutinib 100 mg capsule plus obinutuzumab 1000 mg/40 mL concentrate for solution for infusion	In combination with obinutuzumab for previously untreated CLL/SLL in patients who are unsuitable for fludarabine-based therapy.	Not recommended for subsidy	$3000* (1 Sep 2022)
Ibrutinib 140 mg capsule, and 140 mg, 280 mg and 420 mg tablets	As monotherapy for previously untreated CLL/SLL in patients who are unsuitable for fludarabine-based therapy.	Not recommended for subsidy	$2000 (1 Sep 2022)
Ibrutinib 140 mg capsule, and 140 mg, 280 mg, 420 mg tablets plus rituximab concentrate for infusion (100 mg/10 mL, 500 mg/50 mL)	Ibrutinib in combination with rituximab for previously untreated CLL/SLL.	Not recommended for subsidy	$3000* (1 Sep 2022)
Ibrutinib 140 mg capsule, and 140 mg, 280 mg, 420 mg tablets plus obinutuzumab 1000 mg/40 mL concentrate for solution for infusion	Ibrutinib in combination with obinutuzumab for previously untreated CLL/SLL.	Not recommended for subsidy	$3000* (1 Sep 2022)
Obinutuzumab 1000 mg/40 mL concentrate for solution for infusion	In combination with chlorambucil for previously untreated CLL.	Not recommended for subsidy	$0
Venetoclax 10 mg, 50 mg and 100 mg	For previously untreated CLL in patients who are unsuitable for	MAF (1 Sep 2022)	$5400 (1 Sep 2022)

tablets and obinutuzumab 1000 mg/40 mL concentrate for solution for infusion	fludarabine-based therapy. Maximum treatment duration of obinutuzumab is 6 cycles and venetoclax is 12 months.		
Venetoclax 10 mg, 50 mg and 100 mg tablets	As monotherapy for patients with CLL who are unsuitable for fludarabine-based therapy following combination treatment with obinutuzumab. Maximum treatment duration of obinutuzumab is 6 cycles and venetoclax is 12 months.	MAF (1 Sep 2022)	$3000 (1 Sep 2022)
Relapsed or refractory chronic lymphocytic leukaemia			
Acalabrutinib 100 mg capsule	As monotherapy for relapsed or refractory CLL/SLL in patients who have received at least one prior therapy.	MAF (1 Sep 2022)	$2000 (1 Sep 2022)
Ibrutinib 140 mg capsule, and 140 mg, 280 mg, 420 mg tablets	As monotherapy for relapsed or refractory CLL/SLL in patients who have received at least one prior therapy.	Not recommended for subsidy	$2000 (1 Sep 2022)
Venetoclax 10 mg, 50 mg and 100 mg tablets plus rituximab biosimilar concentrate for infusion (100 mg/10 mL, 500 mg/50 mL)	In combination with rituximab biosimilar (subsidised brand) for patients with relapsed or refractory CLL who have received at least one prior therapy. Maximum treatment duration of rituximab is 6 cycles and venetoclax is 24 months.	MAF (1 Sep 2022)	$3800* (1 Sep 2022)
Venetoclax 10 mg, 50 mg and 100 mg tablets plus rituximab concentrate for infusion (100 mg/10 mL, 500 mg/50 mL)	In combination with rituximab (non-subsidised brand) for patients with relapsed or refractory CLL who have received at least one prior therapy. Maximum treatment duration of rituximab is 6 cycles and venetoclax is 24 months.	Not recommended for subsidy	$3000 (1 Sep 2022)
Venetoclax 10 mg, 50 mg and 100 mg tablets	As monotherapy for patients with relapsed or refractory CLL following combination treatment with rituximab. Maximum treatment duration of rituximab is 6 cycles and venetoclax is 24 months.	MAF (1 Sep 2022)	$3000 (1 Sep 2022)

Abbreviations: CLL, chronic lymphocytic leukaemia; MAF, Medication Assistance Fund; SLL, small lymphocytic lymphoma
*change in MSHL claim limit with effect from 1 Aug 2023

VERSION HISTORY

Guidance on review of cancer drugs for chronic lymphocytic 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 12 July 2022

2. **Guidance updated with the increased MSHL claim limits for several drug combinations**

   Date of Publication 1 Aug 2023

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

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 based on the evidence available to the MOH Drug Advisory Committee as at 27 May 2021 2 July 2021 and 14 April 2023. It 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

Chief HTA Officer
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg