Technology Guidance

[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 2 JANUARY 2024.]

Acalabrutinib, bortezomib and ibrutinib

for treating mantle cell lymphoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Acalabrutinib 100 mg capsule; and
- ✓ Bortezomib 3.5 mg injection

for treating mantle cell lymphoma (MCL) in line with specific clinical criteria.

Subsidy status

Acalabrutinib 100 mg capsule is recommended for inclusion on the Medication Assistance Fund (MAF) for treating patients with MCL who have received at least one prior therapy.

Bortezomib 3.5 mg injection is recommended for inclusion on the MOH Standard Drug List (SDL):

- in combination with rituximab biosimilar (subsidised brand), cyclophosphamide, doxorubicin and prednisone for treating patients with previously untreated MCL who are unsuitable for haematopoietic stem cell transplantation; and
- as monotherapy for treating patients with MCL who have received at least one prior therapy.

SDL subsidy and MAF assistance will be implemented from 1 September 2022.

SDL subsidy and MAF assistance **does not** apply to ibrutinib, or bortezomib when used with non-subsidised brand of rituximab.

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

Updated: 7 December 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 acalabrutinib, bortezomib and ibrutinib for treating mantle cell lymphoma (MCL). 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 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 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 acknowledged that MCL is an uncommon, aggressive subtype of mature B cell non-Hodgkin lymphoma, with approximately 11 new cases diagnosed each year in Singapore. Most patients with MCL (~70%) have advanced disease at diagnosis. While there is no standard of care for treating MCL, the Committee noted that various regimens of chemoimmunotherapy are used in local practice in line with international clinical guidelines.

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2.2. Previously untreated mantle cell lymphoma

The Committee heard that bendamustine plus rituximab (BR) is the most common treatment regimen used in local practice followed by rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), rituximab plus cyclophosphamide, doxorubicin and prednisone with bortezomib (VR-CAP), and rituximab plus bendamustine and cytarabine (R-BAC). The Committee noted that rituximab biosimilar, cyclophosphamide, doxorubicin, and vincristine are already listed on SDL. Bendamustine (generic) has also recently been recommended for listing on SDL.

2.3. Relapsed or refractory mantle cell lymphoma

The Committee noted that patients typically experience disease progression despite initial therapy. In local practice, patients usually receive a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib or acalabrutinib) or bortezomib (~10% of patients who have not received bortezomib previously). The Committee also considered advice from local experts that there was a clinical need to subsidise at least one treatment to improve affordability and ensure appropriate patient care given that none of them are currently included in the MOH List of Subsidised Drugs for this indication, representing a therapeutic gap.

Clinical effectiveness and safety

3.1. Previously untreated mantle cell lymphoma

The Committee reviewed the available clinical evidence for bortezomib in patients with previously untreated MCL for whom haematopoietic stem cell transplantation is unsuitable and acknowledged that the trial results showed statistically significant improvements in overall survival (OS) and progression-free survival (PFS) for VR-CAP (containing bortezomib) compared to R-CHOP (without bortezomib).

3.2. Relapsed or refractory mantle cell lymphoma

The Committee noted that the available clinical evidence (three single-arm studies) for acalabrutinib (ACE-LY-004), bortezomib (PINNACLE) and ibrutinib (PCYC-1104-CA) suggested that all three treatments were effective in treating relapsed or refractory MCL according to the endpoints measured. However, in view of the lack of head-to-head trials comparing the treatments with each other, the Committee concluded that there was no evidence at this time to support the superiority of any drug for this indication.

3.3. The Committee heard that local experts considered ibrutinib and acalabrutinib were clinically comparable in efficacy and safety. However, some patients may experience fewer side effects (e.g., bleeding and atrial fibrillation) with acalabrutinib, compared with ibrutinib.

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Cost effectiveness

4.1. In the absence of a local cost-effectiveness evaluation, the Committee reviewed results from overseas reference HTA agencies and agreed that they were likely to be generalisable to the local context.

4.2. Previously untreated mantle cell lymphoma
The Committee heard that bortezomib (proprietary formulation) was recommended by NICE (UK) for previously untreated MCL in patients for whom haematopoietic stem cell transplantation is unsuitable in view of favourable cost-effectiveness for VR-CAP compared with R-CHOP. The Committee noted that with the availability of a generic formulation of bortezomib in Singapore, it was likely to be at least as cost effective in local practice when used for this indication.

4.3. Relapsed or refractory mantle cell lymphoma
The Committee heard that bortezomib had not been evaluated for relapsed or refractory MCL by most overseas reference HTA agencies. However, given the availability of generic bortezomib locally, the Committee agreed that it was likely to be cost effective for this indication.

4.4. The Committee heard that the PBAC (Australia), NICE (UK) and CADTH (Canada) had recommended listing BTK inhibitors for relapsed or refractory MCL conditional upon a confidential price reduction or risk-sharing agreement with the manufacturer to achieve cost-effectiveness and manage the high and uncertain budget impact associated with the potentially long treatment duration. The Committee acknowledged that BTK inhibitors would unlikely be cost-effective in the local context without a price volume agreement (PVA) in place with the manufacturers.

4.5. The manufacturers of ibrutinib and acalabrutinib were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. A VBP proposal was not requested for bortezomib due to the availability of a generic formulation. The Committee heard that there remained considerable uncertainty regarding the cost-effectiveness and overall budget impact for ibrutinib in the absence of a PVA. The Committee acknowledged that the manufacturer of acalabrutinib proposed a PVA which the Committee considered was acceptable to manage the high and uncertain budget impact, and therefore likely to be considered an acceptable use of healthcare resource in local setting.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact in the first year of listing generic bortezomib on SDL for previously untreated and relapsed or refractory MCL was estimated to be less than SG$1 million based on local epidemiological rates and

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estimated drug utilisation in the public healthcare institutions.

5.2. The annual cost impact in the first year of listing acalabrutinib on MAF for patients with MCL who have received at least one prior therapy was estimated to be less than SG$1 million based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions.

Additional considerations

6.1. The Committee acknowledged that, contingent on subsidy listing, the manufacturer of acalabrutinib had agreed to implement a patient assistance programme (PAP) for eligible patients which would provide further savings in addition to MAF assistance.

Recommendations

7.1. Previously untreated mantle cell lymphoma
The Committee recommended bortezomib 3.5 mg injection be listed on SDL for use in combination with rituximab biosimilar (subsidised brand), cyclophosphamide, doxorubicin and prednisone for treating patients with previously untreated MCL who are unsuitable for haematopoietic stem cell transplantation, in view of acceptable clinical effectiveness and cost effectiveness.

7.2. Relapsed or refractory mantle cell lymphoma
The Committee recommended bortezomib 3.5 mg injection be listed on SDL for treating patients with MCL who have received at least one prior therapy, in view of the current therapeutic gap in the MOH List of Subsidised Drugs and acceptable cost effectiveness.

7.3. In view of the clinical need for treating relapsed or refractory MCL, the Committee recommended acalabrutinib 100 mg capsule be listed on MAF for treating patients with MCL who have received at least one prior therapy, contingent on a PVA being in place with the manufacturer to reduce the uncertainty in the overall budget impact and improve cost-effectiveness.

7.4. In view of uncertainty in cost-effectiveness and the overall budget impact, the Committee did not recommend ibrutinib for listing on MAF.

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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 mantle cell lymphoma			
Bortezomib 3.5 mg injection	Bortezomib in combination with rituximab biosimilar (subsidised brand), cyclophosphamide, doxorubicin and prednisone for the treatment of patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.	SDL[#] (1 Sep 2022)	$1400 (1 Sep 2022)
Relapsed or refractory mantle cell lymphoma			
Acalabrutinib 100 mg capsule	Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.	MAF (1 Sep 2022)	$2000 (1 Sep 2022)
Bortezomib 3.5 mg injection		SDL[#] (1 Sep 2022)	$1400 (1 Sep 2022)
Ibrutinib 140 mg capsule, and 140 mg, 280 mg, 560 mg tablets		Not recommended for subsidy	$2000 (1 Sep 2022)

Abbreviation: SDL, Standard Drug List; MAF, Medication Assistance Fund; PHI, Public Healthcare Institution; [#]removal of brand-specific listing for subsidy with effect from 1 Feb 2023.

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VERSION HISTORY

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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.

Publication of guidance
Date of Publication 12 July 2022

Guidance updated with the following changes:

- removal of brand-specific listing for subsidy for bortezomib

Date of Publication 7 Dec 2022

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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, 28 March 2022 and 8 November 2022. 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

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