Technology Guidance

Review of cancer drugs

for previously treated multiple myeloma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Carfilzomib 30 mg powder for solution for infusion;
- ✓ Ixazomib 3 mg and 4 mg capsules; and
- ✓ Pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules

for previously treated multiple myeloma in line with specific clinical criteria.

Carfilzomib, ixazomib and pomalidomide should be used in line with the recommended treatment regimens listed in the Annex.

Subsidy status

Carfilzomib 30 mg powder for solution for infusion, ixazomib 3 mg and 4 mg capsules and pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules are recommended for inclusion on the Medication Assistance Fund (MAF) in line with the abovementioned indication.

MAF assistance for carfilzomib will be implemented from 4 January 2022. MAF assistance for ixazomib and pomalidomide will be implemented from 1 September 2022.

MAF assistance **does not** apply to daratumumab 100 mg/5 ml and 400 mg/20 ml concentrate for solution for infusion and 1800 mg/15 ml solution for subcutaneous injection when used for previously treated multiple myeloma.

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

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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 carfilzomib, daratumumab, ixazomib and pomalidomide for previously treated multiple myeloma. 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 use of panobinostat for previously treated multiple myeloma was outside the scope of the evaluation following advice from local clinical experts and ODS members who advised that there was no clinical need for this drug to be evaluated. The 60 mg strength of carfilzomib and 2.3 mg strength of ixazomib were excluded from evaluation as they were not commercially available in Singapore at the time of evaluation.

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 approximately 100 patients are diagnosed with multiple myeloma each year in Singapore. Disease progression is common, and most patients will require multiple lines of treatment. The Committee acknowledged that there was a high clinical need to consider treatments for subsidy to improve affordability and ensure appropriate patient care.

2.2. The Committee heard that clinical protocols for multiple myeloma are regularly updated to reflect medical advancements and local clinical experts do not follow a fixed treatment algorithm to manage patients after disease progression. Instead, the

choice of treatment is typically patient-specific depending on multiple factors including tolerability and response to prior treatments, disease activity, patient characteristics and route of administration. Triple therapy with two novel agents (either a proteasome inhibitor, immunomodulatory drug or monoclonal antibody) in combination with a corticosteroid is usually preferred over dual therapy (one novel agent plus corticosteroid) in patients who are able to tolerate the increased side effects. Daratumumab monotherapy is rarely used in local practice.

2.3. The Committee noted that eight HSA-approved treatment regimens were included in ACE's evaluation:

- carfilzomib + lenalidomide + dexamethasone (CLd);
- daratumumab + lenalidomide + dexamethasone (DLd);
- ixazomib + lenalidomide + dexamethasone (ILd);
- daratumumab + bortezomib + dexamethasone (DBd);
- pomalidomide + bortezomib + dexamethasone (PBd);
- carfilzomib + dexamethasone (Cd);
- pomalidomide + dexamethasone (Pd); and
- daratumumab monotherapy.

2.4. The Committee acknowledged that off-label combinations (adding cyclophosphamide to Pd or Cd, and adding thalidomide to Cd) were also used locally and were supported by smaller phase II studies.

Clinical effectiveness and safety

3.1. Carfilzomib, daratumumab and ixazomib in combination with lenalidomide and dexamethasone (CLd, DLd and ILd)

The Committee reviewed three randomised controlled trials (RCTs) which compared CLd (ASPIRE), DLd (POLLUX) and ILd (TOURMALINE-MM1) with lenalidomide plus dexamethasone (Ld) in patients with multiple myeloma after disease progression. All trials showed progression free survival (PFS) benefits favouring the triple therapies compared to dual therapy with Ld. The Committee noted that carfilzomib triple therapy (CLd) led to an improvement in overall survival (OS) after a median follow up of 67 months. OS data were immature for POLLUX (DLd) and TOUMALINE-MM1 (ILd). The Committee acknowledged that the baseline characteristics were different between the RCTs.

3.2. Daratumumab and pomalidomide in combination with bortezomib and dexamethasone (DBd and PBd) and carfilzomib with dexamethasone (Cd)

The Committee reviewed three RCTs which compared DBd (CASTOR), PBd (OPTIMISMM) and Cd with bortezomib + dexamethasone (Bd) in patients with multiple myeloma after disease progression. The studies included varying proportions of patients who were refractory to lenalidomide, with the highest proportion in the OPTIMISMM study. Similarly, all trials showed PFS benefits favouring DBd, PBd and

Cd compared to Bd. The Committee noted that patients treated with Cd had an improvement in OS after a median follow up of 44 months. OS data were immature for CASTOR (DBd) and OPTIMISMM (PBd).

3.3. Pomalidomide in combination with dexamethasone (Pd) and daratumumab monotherapy

The Committee heard that Pd and daratumumab only had HSA approval for later lines of multiple myeloma treatment. The Committee reviewed one RCT (for Pd compared to high-dose dexamethasone) and one single arm study (for daratumumab monotherapy). Results showed Pd led to PFS and OS benefits compared to high-dose dexamethasone. The study for daratumumab monotherapy showed that it led to a median PFS and OS of 3.7 months and 17.5 months, respectively.

3.4. Clinical conclusions

The Committee noted that all combination regimens were associated with different safety and tolerability profiles.

3.5. The Committee acknowledged that there were significant differences in the baseline characteristics of the populations, duration of follow-up and trial designs across all studies, and any indirect treatment comparisons (ITC) would likely be confounded by these differences.

Cost effectiveness

4.1. Carfilzomib, daratumumab and ixazomib in combination with lenalidomide and dexamethasone (CLd, DLd and ILd)

The Committee reviewed an in-house cost effectiveness analysis conducted by ACE comparing CLd, DLd and Ld in patients with previously treated multiple myeloma. At current prices (before value-based pricing (VBP) proposals), results from the analysis showed both CLd and DLd were associated with a base-case incremental cost effectiveness ratio (ICER) of more than SG$105,000 per quality adjusted life year (QALY) gained compared to Ld. The high ICERs were largely due to the higher treatment cost of the triple therapies and significantly longer duration of treatment compared with Ld. There was also significant uncertainty in the magnitude of QALYs gained given the long extrapolation of the OS KM curve.

4.2. Following VBP negotiations, the cost-effectiveness of CLd was improved and considered to be acceptable by the Committee. They also noted that the price proposed for carfilzomib was comparable with overseas reference jurisdictions. The price proposed by the manufacturer for ixazomib was also comparable to carfilzomib and overseas reference jurisdictions. The Committee noted that the price proposed by the manufacturer of daratumumab was higher than overseas reference jurisdictions, and the ICER for DLd remained high and was not considered to be cost effective compared to Ld based on the local cost effectiveness analysis. The

treatment cost of DLd was also higher than CLd and ILd.

4.3. Daratumumab and pomalidomide in combination with bortezomib and dexamethasone (DBd and PBd) and carfilzomib with dexamethasone (Cd)
The Committee noted that the price proposed by the manufacturer for pomalidomide was comparable with overseas reference jurisdictions. The manufacturer also agreed to enter into a confidential price volume agreement (PVA) which reduced the uncertainty of the overall budget impact and further improved cost-effectiveness. Therefore, the Committee considered PBd was likely to represent a cost-effective option for previously treated multiple myeloma in the local context. The Committee noted the cost of treatment with Cd was the lowest among all the combination regimens evaluated. The cost of treatment with DBd was significantly higher than PBd and Cd, and therefore, it was not considered to represent a cost-effective option.

4.4. The Committee considered that any additional costs from off-label use of cyclophosphamide or thalidomide added on to Cd and Pd would be low, and hence these combination regimens were also likely to be cost-effective in the local setting.

4.5. Pomalidomide in combination with dexamethasone (Pd) and daratumumab monotherapy
The Committee noted the cost of treatment with Pd was lower than daratumumab monotherapy, and therefore considered that Pd represented a cost-effective treatment option.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact in the first year of listing carfilzomib and ixazomib on MAF for previously treated multiple myeloma was estimated to be less than SG$1 million each, while for pomalidomide, the annual cost impact was estimated to be between SG$1 million to less than SG$3 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 carfilzomib had agreed to offer free home administrations to patients who are able to receive treatment at home, which would provide further savings to eligible patients.

Recommendations

7.1. Based on available evidence, the Committee recommended carfilzomib, ixazomib and pomalidomide be listed on MAF for patients with previously treated multiple myeloma, in view of the high clinical need for subsidised options, and acceptable clinical effectiveness and cost effectiveness at the prices proposed by the manufacturers. The recommended treatment regimens are listed in the Annex.

7.2. At the price proposed by the manufacturer, daratumumab (either in combination with lenalidomide and dexamethasone; bortezomib and dexamethasone, or as monotherapy) was not recommended for listing on MAF for patients with previously treated multiple myeloma due to unacceptable cost effectiveness compared with the other treatment options.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Carfilzomib 30 mg powder for solution for infusion	Carfilzomib in combination with lenalidomide or thalidomide or cyclophosphamide, plus dexamethasone, for patients with multiple myeloma who have received at least one prior therapy. Treatment with carfilzomib should be stopped after 18 cycles, or earlier if disease progresses.	MAF (4 Jan 2022)	$2000 (1 Sep 2022)
Carfilzomib 30 mg powder for solution for infusion	Carfilzomib in combination with dexamethasone for patients with multiple myeloma who have received at least one prior therapy.	MAF (4 Jan 2022)	$2000 (1 Sep 2022)
Daratumumab 100 mg/5 ml and 400 mg/20 ml concentrate for solution for infusion and 1800 mg/15 ml solution for subcutaneous injection	Daratumumab in combination with lenalidomide and dexamethasone for patients with multiple myeloma who have received at least one prior therapy.	Not recommended for subsidy	$2000 (1 Sep 2022)
Daratumumab 100 mg/5 ml and 400 mg/20 ml concentrate for solution for infusion and 1800 mg/15 ml	Daratumumab in combination with bortezomib and dexamethasone for patients with multiple myeloma who	Not recommended for subsidy	$2000 (1 Sep 2022)

solution for subcutaneous injection	have received at least one prior therapy.		
Daratumumab 100 mg/5 ml and 400 mg/20 ml concentrate for solution for infusion and 1800 mg/15 ml solution for subcutaneous injection	Daratumumab as monotherapy, for patients with multiple myeloma who have received at least three prior therapies including a proteasome inhibitor and an immunomodulator.	Not recommended for subsidy	Not recommended for MediShield Life claims
Ixazomib 3 mg and 4 mg capsules	Ixazomib in combination with lenalidomide and dexamethasone for patients with multiple myeloma who have received at least one prior therapy.	MAF (1 Sep 2022)	$2000 (1 Sep 2022)
Pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules	Pomalidomide in combination with bortezomib or cyclophosphamide, plus dexamethasone, for patients with multiple myeloma who have received at least one prior therapy.	MAF (1 Sep 2022)	$2000 (1 Sep 2022)
Pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules	Pomalidomide in combination with dexamethasone for patients with multiple myeloma who have received at least two prior therapies, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	MAF (1 Sep 2022)	$2000 (1 Sep 2022)

Abbreviations: SDL, Standard Drug List; MAF, Medication Assistance Fund.

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 16 March 2021, 27 May 2021, 2 July 2021 and 26 November 2021. 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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