Technology Guidance

Aflibercept, bevacizumab and ramucirumab

for treating metastatic colorectal cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended aflibercept, bevacizumab reference biologic (Avastin) or ramucirumab for subsidy for treating metastatic colorectal cancer.

Bevacizumab (Avastin) has not been recommended in view of unfavourable cost effectiveness compared with bevacizumab biosimilar (Mvasi) at the price proposed by the manufacturer.

Aflibercept has not been recommended due to low clinical need and unfavourable cost effectiveness compared with Mvasi.

Ramucirumab has not been recommended following a request from the manufacturer to not consider it for subsidy.

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

Updated: 1 June 2026

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of anti-vascular endothelial growth factor (VEGF) agents (aflibercept, bevacizumab and ramucirumab) for treating metastatic colorectal cancer. 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.

1.4. The technology evaluation of bevacizumab biosimilar (Mvasi) for treating different types of cancer in line with its registered indications is discussed in a separate guidance.

Clinical need

2.1. Approximately 2130 patients are diagnosed with colorectal cancer each year in Singapore. For metastatic colorectal cancer (mCRC) that is previously untreated or has progressed after first-line systemic therapy, chemotherapy or bevacizumab in combination with chemotherapy represent standard of care in local practice, in line with international clinical guidelines.

2.2. The Committee heard that aflibercept and ramucirumab, both used in combination with FOLFIRI, are also approved by HSA for treating mCRC that has progressed after first-line therapy, however, they are not commonly used in local practice and there was low clinical need to consider them for subsidy at this time.

2.3. While chemotherapy regimens (e.g., CAPOX, FOLFIRI and FOLFOX) are already subsidised for treating mCRC, the Committee acknowledged the clinical need to consider bevacizumab for subsidy to allow flexibility in treatment protocols and improve affordability for patients.

Clinical effectiveness and safety

3.1. Previously untreated mCRC

The Committee reviewed the clinical evidence from six randomised controlled trials (RCTs) that investigated the use of bevacizumab in patients with previously untreated mCRC. Four of the RCTs (ITACa, NO16966, MAX and AVEX) compared bevacizumab in combination with fluoropyrimidine-based chemotherapy (FOLFIRI, FOLFOX4, CAPOX or capecitabine) versus chemotherapy alone. While bevacizumab plus chemotherapy did not show overall survival (OS) benefit in any trial, it improved progression-free survival (PFS) compared to chemotherapy alone in three of the trials.

3.2. Two of the RCTs (AVF2107g and ARTIST) investigated bevacizumab in combination with chemotherapy regimens involving bolus administration of fluorouracil (5-FU) or leucovorin. Both trials showed OS benefit with bevacizumab plus chemotherapy compared to chemotherapy alone. However, the Committee noted that bolus 5-FU/leucovorin regimens are less preferred in current practice as they are associated with higher toxicity compared to infused regimens.

3.3. The Committee reviewed the results of a meta-analysis considered by PHARMAC (New Zealand) which suggested that bevacizumab provided more benefit when it was used with less effective chemotherapy (e.g. capecitabine monotherapy), rather than with more effective standard of care combinations (e.g. FOLFIRI and FOLFOX).

3.4. In terms of safety, bevacizumab was associated with adverse events of hypertension, haemorrhage, gastrointestinal perforations, fistulae, thromboembolism, proteinuria, neutropenia, and wound healing complications.

3.5. Overall, the Committee considered that a modest clinical benefit was provided when bevacizumab was added to standard of care chemotherapy regimens in patients with previously untreated mCRC.

3.6. Metastatic CRC that has progressed after first-line systemic therapy

The Committee reviewed the clinical evidence from three RCTs for bevacizumab (E3200, ML18147 and BEBYP), and one RCT each for aflibercept (VELOUR) and ramucirumab (RAISE) in patients with mCRC that had progressed after first-line therapy.

3.7. The E3200 trial for bevacizumab was conducted in bevacizumab-naïve patients whose disease had progressed after first-line treatment with a fluoropyrimidine and irinotecan. The results showed that bevacizumab plus FOLFOX4 led to an improvement in median OS of 2.2 months compared to FOLFOX4 alone.

3.8. The ML18147 and BEBYP trials for bevacizumab were conducted in patients whose disease had progressed after first-line bevacizumab plus chemotherapy (including a fluoropyrimidine with either oxaliplatin or irinotecan). The ML18147 trial showed that bevacizumab plus chemotherapy led to an improvement in median OS of 1.4 months compared to chemotherapy alone. In view of this positive finding, the similarly-designed BEBYP trial was stopped prematurely and its results could not be meaningfully interpreted.

3.9. The VELOUR trial for aflibercept was conducted in patients whose disease had progressed after first-line oxaliplatin-based chemotherapy with or without bevacizumab. The results showed that aflibercept plus FOLFIRI led to an improvement in median OS of 1.4 months compared to FOLFIRI alone. In terms of safety, aflibercept showed a similar toxicity profile compared with bevacizumab, but it also increased the incidence of some chemotherapy-related adverse events such as diarrhoea, asthenia, stomatitis and infections.

3.10. The RAISE trial for ramucirumab was conducted in patients whose disease had progressed after first-line therapy with bevacizumab, oxaliplatin and a fluoropyrimidine. The results showed that ramucirumab plus FOLFIRI led to an improvement in median OS of 1.6 months compared to FOLFIRI alone. In terms of safety, ramucirumab was associated with similar types of adverse events as bevacizumab.

3.11. Overall, the Committee considered that there was sufficient clinical evidence to support the use of aflibercept, bevacizumab and ramucirumab for treating mCRC that has progressed after first-line therapy. However, in the absence of head-to-head studies, a recommendation on the superiority of one drug over another could not be concluded.

Cost effectiveness

4.1. The manufacturers of aflibercept, bevacizumab reference biologic (Avastin), and ramucirumab were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. The manufacturer of ramucirumab did not submit a pricing proposal, indicating that they did not want their product reviewed for subsidy consideration.

4.2. Previously untreated mCRC

In the absence of local economic analyses for bevacizumab, the Committee reviewed evaluations from overseas HTA agencies. They noted that NICE (UK) and CADTH (Canada) did not consider Avastin plus chemotherapy to be cost-effective compared to chemotherapy alone for previously untreated mCRC. These conclusions were considered to be generalisable to the Singapore setting, as the prices of bevacizumab used in the evaluations were lower than the local cost of Avastin.

4.3. The Committee acknowledged that they had established therapeutic equivalence between bevacizumab reference biologic (Avastin) and bevacizumab biosimilar (Mvasi) in a separate technology evaluation, and that a cost-minimisation approach was appropriate to assess the cost effectiveness of Avastin. At the price proposed by the manufacturer, Avastin did not represent a cost-effective treatment option compared to Mvasi.

4.4. Metastatic CRC that has progressed after first-line systemic therapy

No local economic analyses for aflibercept, bevacizumab and ramucirumab were identified for metastatic CRC that has progressed after first-line therapy. The Committee noted that NICE (UK) did not consider Avastin plus chemotherapy to be cost-effective compared to chemotherapy alone for previously treated mCRC, and this conclusion was likely to be generalisable to Avastin in the Singapore setting.

4.5. The Committee reviewed evaluations from overseas HTA agencies for aflibercept for previously treated mCRC. However, given that the drug prices used in the evaluations were not published or had included confidential discounts from the manufacturer, it was unknown whether the prices were comparable to those in Singapore and if the results were generalisable. For ramucirumab, no evaluation by overseas HTA agencies was identified for this indication.

4.6. The Committee noted that the average monthly cost of Mvasi was lower compared to aflibercept for previously treated mCRC. Hence, aflibercept was not considered to be a cost-effective treatment option compared to Mvasi on a cost-minimisation basis.

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 bevacizumab reference biologic (Avastin) or aflibercept on the MOH Standard Drug List (SDL) or Medication Assistance Fund (MAF) for treating metastatic colorectal cancer was estimated to be:

- Bevacizumab (Avastin): between SG$5 million to less than SG$10 million; and
- Aflibercept: less than SG$1 million.

Recommendations

6.1. Based on available evidence, the Committee did not recommend bevacizumab reference biologic (Avastin) for subsidy for treating metastatic colorectal cancer, due to unfavourable cost effectiveness compared with bevacizumab biosimilar (Mvasi) at the price proposed by the manufacturer.

6.2. The Committee noted that Mvasi had been recommended for listing on the SDL for treating different types of cancer, including metastatic colorectal cancer, as part of a separate review, with subsidy implementation effective from 1 April 2022.

6.3. The Committee did not recommend aflibercept for subsidy due to low clinical need and unfavourable cost effectiveness compared with Mvasi. Ramucirumab was not recommended following a request from the manufacturer to not consider their product for subsidy.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Approved clinical indications	Subsidy class (implementation date)	Eligible for MediShield Life claims (implementation date)
Aflibercept 100 mg/4 mL concentrate for solution for infusion	Aflibercept in combination with FOLFIRI for treating metastatic colorectal cancer that has progressed on first-line systemic therapy.	Not recommended for subsidy	Yes[1] (1 Sep 2022)
Bevacizumab biosimilar (Mvasi) 100 mg/4 mL and 400 mg/16 mL concentrate for solution for infusion	Bevacizumab biosimilar in combination with fluoropyrimidine-based chemotherapy for treating metastatic colorectal cancer.	SDL (1 Apr 2022)	Yes[1] (1 Sep 2022)
Bevacizumab reference biologic (Avastin) 100 mg/4 mL and 400 mg/16 mL concentrate for solution for infusion	Bevacizumab in combination with fluoropyrimidine-based chemotherapy for treating metastatic colorectal cancer.	Not recommended for subsidy	Yes[1] (1 Sep 2022)
Ramucirumab 100 mg/10 mL and 500 mg/50 mL concentrate for solution for infusion	Ramucirumab in combination with FOLFIRI for treating metastatic colorectal cancer that has progressed on first-line systemic therapy.	Not recommended for subsidy	Yes[1] (1 Sep 2022)

Abbreviation: SDL, Standard Drug List.
[1] Please refer to MOH's website for the MediShield Life claim limit starting from the implementation date.

VERSION HISTORY

Guidance on aflibercept, bevacizumab and ramucirumab for treating metastatic colorectal cancer

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 Apr 2022

2. **Guidance updated with the MediShield Life claim limits for aflibercept and bevacizumab**
   Date of Publication 12 Jul 2022

3 **Guidance updated to reflect MediShield Life claims eligibility**
   Date of Publication 1 Jun 2026

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 funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The 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 https://www.ace-hta.gov.sg/about-us/

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