Technology Guidance

Regorafenib and trifluridine/tipiracil

for previously treated metastatic colorectal cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Regorafenib 40 mg tablet for treating patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, and if RAS wild-type, anti-EGFR therapy.

Subsidy status

Regorafenib 40 mg tablet is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication with effect from 4 January 2022.

MAF assistance **does not** apply to any formulations or strengths of trifluridine/tipiracil.

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

Updated: 19 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 regorafenib and trifluridine/tipiracil combination product (Lonsurf) for treating metastatic colorectal cancer that has progressed after two or more lines of systemic therapy. 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 both 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. Approximately 2,130 patients are diagnosed with colorectal cancer each year in Singapore. For patients who have metastatic colorectal cancer (mCRC) that has progressed after two or more lines of systemic therapy, regorafenib and trifluridine/tipiracil are standard of care in local practice, in line with international guidelines. The Committee acknowledged the clinical need to consider these drugs for subsidy to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

3.1. The Committee reviewed two randomised placebo-controlled trials each for regorafenib and trifluridine/tipiracil in patients with mCRC that had progressed after two or more lines of systemic treatment. The prior therapies could include

fluoropyrimidine, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor (VEGF) therapy, and if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy. For both regorafenib and trifluridine/tipiracil, a global trial as well as Asian trial were conducted.

3.2. Regorafenib showed an overall survival (OS) benefit over placebo in both trials, with a larger improvement in median OS observed in the Asian CONCUR trial compared to the global CORRECT trial (2.5 months vs. 1.4 months, respectively). Common adverse reactions reported with regorafenib included hand-foot skin reaction, asthenia/fatigue, diarrhoea, hypertension and hyperbilirubinaemia.

3.3. For trifluridine/tipiracil, an OS benefit was shown over placebo in both trials, with a larger improvement in median OS observed in the global RECOURSE trial compared to the Asian TERRA trial (1.8 months vs. 0.7 months, respectively). Common adverse reactions reported with trifluridine/tipiracil included anaemia, neutropenia, asthenia/fatigue, nausea and thrombocytopenia.

3.4. Due to heterogeneity of the trial populations, the Committee noted that the comparative effectiveness and safety of regorafenib versus trifluridine/tipiracil could not be determined. In the absence of a head-to-head study, both drugs were considered to be clinically comparable for treating mCRC.

Cost effectiveness

4.1. The manufacturers of regorafenib and trifluridine/tipiracil were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. No local cost-effectiveness analyses for regorafenib or trifluridine/tipiracil in patients with mCRC were identified. Hence, the Committee reviewed evaluations from overseas HTA agencies, but noted that the drug costs used in their analyses were not published or had included confidential discounts from manufacturers. Therefore, it was unknown whether the overseas prices were comparable to those in Singapore and if the results were generalisable.

4.2. The Committee noted that at the local proposed prices, the monthly treatment cost of regorafenib was lower than that of trifluridine/tipiracil. The price of regorafenib was also comparable to prices in overseas reference jurisdictions, while the price of trifluridine/tipiracil was higher than overseas prices.

4.3. Therefore, the Committee agreed that regorafenib was likely to represent a cost-effective treatment for mCRC, while trifluridine/tipiracil was not considered to be cost-effective versus regorafenib 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 regorafenib on MAF for treating mCRC was estimated to be between SG$1 million to less than SG$3 million.

Recommendations

6.1. Based on available evidence, the Committee recommended regorafenib 40 mg tablet be listed on MAF for treating mCRC that has progressed after two or more lines of systemic therapy, in view of clinical need, and favourable clinical and cost-effectiveness.

6.2. The Committee did not recommend trifluridine/tipiracil for listing on MAF due to unfavourable cost-effectiveness compared with regorafenib at the proposed prices.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Regorafenib 40 mg tablet	Treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, and if RAS wild-type, anti-EGFR therapy.‡	MAF (4 Jan 2022)	$1800 (1 Sep 2022)
Trifluridine/tipiracil 15 mg/6.14 mg and 20 mg/8.19 mg tablets	Treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, and if RAS wild-type, anti-EGFR therapy. ‡	Not recommended for subsidy	$1800 (1 Sep 2022)

Abbreviation: MAF, Medication Assistance Fund.
‡revised clinical indication with effect from 1 Feb 2023

VERSION HISTORY

Guidance on regorafenib and trifluridine/tipiracil for previously treated 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 4 Jan 2022

2. **Guidance updated to revise the clinical indications for regorafenib and trifluridine/tipiracil to include patients who are not considered candidates for available therapies**

   Date of Publication 19 Dec 2022

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, 2 July 2021 and 2 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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