Technology Guidance

Cetuximab and panitumumab

for treating RAS wild-type colorectal cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Cetuximab 100 mg/20 mL solution for infusion; and
- ✓ Panitumumab 100 mg/5 mL concentrate for solution for infusion

as monotherapy or in combination with chemotherapy for treating RAS wild-type metastatic colorectal cancer.

Subsidy status

Panitumumab 100 mg/5 mL concentrate for solution for infusion is recommended for inclusion on the MOH Standard Drug List (SDL) for the abovementioned indication with effect from 4 January 2022.

Cetuximab 100 mg/20 mL solution for infusion is recommended for inclusion on the SDL for the abovementioned indication with effect from 1 September 2022.

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

Updated: 12 July 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 cetuximab and panitumumab for treating RAS wild-type metastatic colorectal cancer (mCRC) in 2021. 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.

1.4. Following a negative recommendation in 2021 due to unfavourable cost-effectiveness, the manufacturer of cetuximab submitted a revised price proposal, which the Committee considered in March 2022.

Clinical need

2.1. Approximately 2,130 patients are diagnosed with colorectal cancer each year in Singapore, of which 50% develop metastatic disease. Prior to beginning treatment, patients with mCRC are routinely tested for the presence of RAS mutations, and approximately 50% of them have RAS wild-type tumours.

2.2. The Committee acknowledged that the anti-epidermal growth factor receptor (EGFR) agents, cetuximab and panitumumab, used as monotherapy or in combination with chemotherapy, are standard of care for previously untreated or treatment-experienced patients with RAS wild-type mCRC, in line with international clinical guidelines.

2.3. The Committee acknowledged the clinical need to consider cetuximab and panitumumab for subsidy to improve treatment affordability and ensure appropriate patient care. In addition, they noted that bevacizumab, chemotherapy, regorafenib, and trifluridine/tipiracil are also commonly used in local practice to treat mCRC regardless of RAS mutation status.

Clinical effectiveness and safety

3.1. Previously untreated RAS wild-type mCRC

The Committee reviewed six randomised controlled trials (RCTs) that investigated the use of cetuximab or panitumumab in combination with chemotherapy (FOLFOX or FOLFIRI). One of the trials involving cetuximab (TAILOR) specifically enrolled patients with RAS wild-type mCRC. The other trials involving cetuximab (CRYSTAL, FIRE-3 and CALGB-80405) or panitumumab (PRIME and PEAK) enrolled patients with EGFR-positive or KRAS wild-type mCRC but conducted subgroup analyses in patients with RAS wild-type tumours.

3.2. The results of these RCTs consistently showed overall survival (OS) benefit with cetuximab or panitumumab in combination with chemotherapy versus chemotherapy alone in patients with RAS wild-type mCRC. When compared with bevacizumab plus chemotherapy combination treatment, cetuximab plus chemotherapy showed OS benefit in one out of two trials, while panitumumab plus chemotherapy did not show OS benefit.

3.3. The Committee noted the results of a network meta-analysis (NMA) considered by NICE (UK), which suggested that cetuximab and panitumumab were comparable in clinical effectiveness for treating RAS wild-type mCRC in previously untreated patients. In a meta-analysis considered by PBAC (Australia), cetuximab was non-inferior in clinical effectiveness and safety to bevacizumab for treating RAS wild-type mCRC, although the two drugs had different safety profiles.

3.4. The Committee noted the results of published post hoc subgroup analyses which suggested that mCRC originating on the right side of the colon was unlikely to respond to first-line anti-EGFR therapy. As such, the use of cetuximab and panitumumab in the first-line setting is mainly limited to left-sided tumours in local practice. However, in view of the uncertainty associated with post hoc analyses, the Committee considered that until conclusive evidence is available, subsidy of anti-EGFR agents should not be restricted to left-sided mCRC in the first-line setting, in line with the approach taken by overseas HTA agencies.

3.5. The Committee heard that cetuximab and panitumumab are approved by HSA for administration once a week and every 2 weeks, respectively. However, in local practice, cetuximab is usually given every 2 weeks to reduce administration costs. Given that the evidence supporting the 2-weekly regimen for cetuximab was derived from phase II exploratory trials only, the Committee considered that there was insufficient evidence to recommend this regimen at this time.

3.6. RAS wild-type mCRC that has progressed after one or more lines of systemic therapy
The Committee reviewed five RCTs (20050181, CO.17, 20020408, 20100007 and ASPECCT) involving cetuximab or panitumumab which enrolled patients with EGFR-positive or KRAS wild-type/mutant mCRC. Only two of the trials (20050181 and 20100007), both involving panitumumab, conducted subgroup analyses in patients with RAS wild-type tumours. The analyses showed that in patients who had been treated with one prior fluoropyrimidine-based chemotherapy regimen, panitumumab plus FOLFIRI improved progression-free survival (PFS), but not overall survival, compared with FOLFIRI. In patients previously treated with oxaliplatin- and irinotecan-based therapies, panitumumab plus best supportive care (BSC) led to an OS benefit compared with BSC alone.

3.7. The Committee considered a head-to-head trial (ASPECCT) comparing panitumumab monotherapy with cetuximab monotherapy in patients with KRAS wild-type mCRC who had been previously treated with oxaliplatin- and irinotecan-based therapies. The results showed that panitumumab was non-inferior in OS to cetuximab, and the overall toxicity was similar between treatment groups. However, no subgroup results for patients with RAS wild-type mCRC were reported.

3.8. Clinical conclusions
The Committee acknowledged the limitations of the clinical trial results which were mostly derived from subgroup analyses. However, in view of the totality of evidence, local clinical experience, and recommendations by international clinical guidelines, the Committee agreed that cetuximab and panitumumab were effective treatments for RAS wild-type mCRC in previously untreated and treatment-experienced patients.

3.9. The Committee considered both drugs to be comparable in effectiveness and safety based on evidence from the ASPECCT trial and in line with local expert opinion.

Cost effectiveness

4.1. In the absence of local economic studies for cetuximab and panitumumab, the Committee reviewed evaluations from overseas HTA agencies. They noted that the drug costs used in the evaluations were not published or had included confidential discounts from manufacturers. Therefore, it was unknown whether the prices were comparable to those in Singapore and if the results were generalisable.

4.2. The manufacturers of cetuximab and panitumumab were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. The Committee noted that at the prices proposed in 2021, the monthly treatment cost of panitumumab was lower than that of cetuximab, regardless of whether it was dosed weekly or 2-weekly. Panitumumab was also competitively priced compared with overseas reference jurisdictions; therefore, the Committee considered that it was likely to be an acceptable use of healthcare resources in the local setting and an SDL listing was appropriate. The Committee considered that cetuximab was not cost-effective versus panitumumab on a cost-minimisation basis.

4.3. In March 2022, following a revised price proposal from the manufacturer, the Committee agreed that the treatment cost of cetuximab was reasonable and could be considered an acceptable use of healthcare resources.

Estimated annual technology cost

5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual combined cost impact in the first year of listing cetuximab and panitumumab on SDL for treating RAS wild-type mCRC was estimated to be between SG$1 million to less than SG$3 million.

Recommendations

6.1. In 2021, the Committee recommended panitumumab 100 mg/5 mL concentrate for solution for infusion be listed on SDL for treating RAS wild-type mCRC, in view of the therapeutic gap in the MOH List of Subsidised Drugs and favourable clinical and cost-effectiveness. Cetuximab was not recommended for subsidy due to unfavourable cost-effectiveness compared to panitumumab at the proposed prices.

6.2. In March 2022, the Committee recommended cetuximab 100 mg/20 mL solution for infusion be listed on SDL for treating RAS wild-type mCRC following an acceptable price proposal from the manufacturer which improved its cost-effectiveness.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Panitumumab 100 mg/5 mL concentrate for solution for infusion	Panitumumab as monotherapy or in combination with chemotherapy for treating RAS wild-type metastatic colorectal cancer.	SDL (4 Jan 2022)	$1000 (1 Sep 2022)
Cetuximab 100 mg/20 mL solution for infusion	Cetuximab as monotherapy or in combination with chemotherapy for treating RAS wild-type metastatic colorectal cancer.	SDL (1 Sep 2022)	$1000 (1 Sep 2022)

Abbreviation: SDL, Standard Drug List.

VERSION HISTORY

Guidance on cetuximab and panitumumab for treating RAS wild-type 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 extend SDL listing to cetuximab**
   Date of Publication 12 Jul 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 18 March 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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