Technology Guidance

Zolbetuximab

for untreated HER2-negative, claudin-18.2-positive, unresectable advanced gastric or gastroesophageal junction adenocarcinoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended zolbetuximab, in combination with chemotherapy, for inclusion on the MOH List of Subsidised Drugs for untreated HER2-negative, claudin-18.2-positive, unresectable advanced gastric or gastroesophageal junction adenocarcinoma. The decision was based on the unfavourable cost effectiveness of zolbetuximab plus chemotherapy compared with alternative treatments, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claims eligibility for zolbetuximab plus chemotherapy are provided in the Annex.

Updated: 1 July 2026

Technology Evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for untreated human epidermal growth factor receptor 2 (HER2)-negative, claudin (CLDN) 18.2-positive, locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. The evaluation considered the company's evidence submission by Astellas for zolbetuximab (Vyloy), and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from clinicians at public healthcare institutions and the MOH Cancer Drug Subcommittee helped ACE ascertain the clinical value of zolbetuximab. Local patient and voluntary organisations were also invited to provide their lived experiences to inform the evaluation, however, no submissions were received.

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 funding considerations.

Clinical need

2.1. In Singapore, approximately 280 patients are diagnosed each year with HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. The current standard first-line systemic therapy for these patients consists of chemotherapy, either alone or in combination with a programmed cell death protein 1 (PD-1) inhibitor.

2.2. Approximately 42% of these patients have tumours that are CLDN18.2-positive (defined as expression in ≥75% of tumour cells). For this subset, zolbetuximab plus chemotherapy is an alternative first-line treatment option. Zolbetuximab is a monoclonal antibody that selectively targets the CLDN18.2 protein to induce cancer cell death.

2.3. In the company's submission for zolbetuximab plus chemotherapy, the nominated comparators were chemotherapy with and without nivolumab. The Committee considered these subsidised treatments to be appropriate comparators. They also considered tislelizumab (another PD-1 inhibitor) plus chemotherapy to be a near-market comparator, as this treatment was recently approved by the HSA for first-line systemic treatment of HER2-negative gastric or GEJ adenocarcinoma with a PD-L1 expression ≥1%.

Clinical effectiveness and safety

3.1. Randomised controlled trials (RCTs)
The Committee reviewed the clinical evidence from two phase III RCTs (GLOW and SPOTLIGHT) that studied zolbetuximab in patients with untreated HER2-negative, CLDN18.2-positive, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.

3.2. Patients in both trials were randomised to receive zolbetuximab or placebo, both in combination with chemotherapy. The chemotherapy regimens used were capecitabine and oxaliplatin (CAPOX) in the GLOW trial, and modified folinic acid, fluorouracil and oxaliplatin regimen (mFOLFOX6) in the SPOTLIGHT trial.

3.3. Results of both trials showed that zolbetuximab improved overall survival (OS) and progression-free survival (PFS) compared with placebo (Table 1).

Table 1: Results of OS and PFS in GLOW and SPOTLIGHT trials

Outcome	Trial [a]	Median (95% CI), in months		HR (95% CI)
		Zolbetuximab	Placebo	
OS	GLOW	14.32 (12.09 to 16.39)	12.16 (10.28 to 13.67)	0.76 (0.62 to 0.94)
	SPOTLIGHT	18.23 (16.13 to 20.63)	15.57 (13.67 to 16.92)	0.78 (0.64 to 0.95)
PFS	GLOW	8.21 (7.26 to 8.84)	6.80 (6.14 to 8.08)	0.69 (0.55 to 0.86)
	SPOTLIGHT	11.04 (9.69 to 12.52)	8.94 (8.21 to 10.41)	0.73 (0.59 to 0.91)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a] Data cutoff dates: 12 January 2024 (GLOW), and 8 September 2023 (SPOTLIGHT).

3.4. Compared to the placebo group, the zolbetuximab group had higher incidence of grade 3 or 4 treatment-related adverse events (TRAEs) and TRAEs leading to treatment discontinuation. Among the grade 3 or 4 TRAEs, nausea and vomiting were most frequently reported with zolbetuximab.

3.5. The submission claimed that zolbetuximab plus chemotherapy was superior in clinical effectiveness compared with chemotherapy alone, which the Committee considered reasonable. In terms of safety, the submission did not make a clinical claim; however, the Committee considered zolbetuximab plus chemotherapy to be inferior to chemotherapy alone based on the trial evidence.

3.6. Indirect treatment comparisons

In the absence of head-to-head trials between zolbetuximab and PD-1 inhibitors, the submission presented a Bayesian network meta-analysis (NMA) that compared the treatment effects of zolbetuximab and nivolumab. The NMA also included a comparison against tislelizumab, although this was not a nominated comparator in the submission.

3.7. The NMA was informed by clinical evidence from two RCTs for zolbetuximab (GLOW and SPOTLIGHT), two RCTs for nivolumab (CheckMate 649 and ATTRACTION-4), and one RCT for tislelizumab (RATIONALE-305). The Committee noted heterogeneity across RCTs (e.g. in study designs, chemotherapy backbones, and patient baseline PD-L1 status), which introduced considerable uncertainty in the NMA results.

3.8. Based on results from the intention-to-treat populations of the RCTs, the NMA showed no significant differences between zolbetuximab and nivolumab or tislelizumab for both OS and PFS outcomes, as the 95% credible intervals of the hazard ratios included 1 in all analyses.

3.9. In terms of safety, the proportion of patients with ≥1 TRAE and the incidence of serious TRAEs were comparable among zolbetuximab, nivolumab, and tislelizumab. However, the treatments had different safety profiles. The most common grade 3 or 4 TRAEs were nausea and vomiting for zolbetuximab, compared with neutropenia and decreased neutrophil count for the PD-1 inhibitors. The Committee noted that while the gastrointestinal toxicities associated with zolbetuximab might have a more direct impact on patients' quality of life, these toxicities could be reduced with prophylactic anti-emetic pre-medications.

3.10. The submission described zolbetuximab as comparable or favourable in clinical effectiveness and safety compared with nivolumab. The Committee considered that, based on available evidence, a claim of non-inferior clinical effectiveness and safety was more appropriate for zolbetuximab versus nivolumab as well as tislelizumab.

Cost effectiveness

4.1. The submission presented a cost-minimisation analysis (CMA) between zolbetuximab and nivolumab based on non-inferiority in clinical effectiveness and safety. No economic analysis against tislelizumab or chemotherapy was included.

4.2. The submission's CMA showed that the total costs associated with zolbetuximab treatment were equal to those associated with nivolumab. However, the Committee considered the results highly uncertain due to issues such as:

- Inappropriate assumptions regarding the mean treatment duration and relative dose intensity for nivolumab;
- Overestimation of nivolumab vial costs;
- Underestimation of CLDN18.2 testing costs; and
- Exclusion of anti-emetic pre-medication costs for zolbetuximab.

4.3. In a reanalysis that addressed the above issues, the total costs for zolbetuximab were higher, compared with nivolumab, when both were assessed over the mean treatment durations reported in the GLOW and SPOTLIGHT trials.

4.4. In a similar CMA conducted by ACE for zolbetuximab versus tislelizumab, the total costs were also shown to be higher with zolbetuximab.

4.5. Overall, the Committee considered that, at the price proposed by the company, zolbetuximab did not represent a cost-effective use of healthcare resources when used with chemotherapy for untreated HER2-negative, CLDN18.2-positive, unresectable advanced gastric or GEJ adenocarcinoma.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would increase from between SG$1 million and SG$3 million in the first year to between SG$3 million and SG$5 million in the fifth year of listing zolbetuximab on the MOH List of Subsidised Drugs for untreated HER2-negative, CLDN18.2-positive, unresectable advanced gastric or GEJ adenocarcinoma.

5.2. The Committee considered that the submission estimates were high due to an overestimation of the proportion of patients with adenocarcinoma histology among all gastric or GEJ cancer cases. The submission also applied inappropriate assumptions regarding the mean treatment duration of zolbetuximab, which overestimated the treatment costs. In addition, there was uncertainty in the uptake rate of zolbetuximab in local clinical practice.

5.3. In a revised budget impact model that addressed these issues and applied a conservative uptake rate, the annual cost impact to the public healthcare system was estimated to be less than SG$1 million in the first five years of listing zolbetuximab on the MOH List of Subsidised Drugs. When a higher uptake rate was assumed, the annual cost impact increased from less than SG$1 million in the first year to between SG$1 million and SG$3 million in the fifth year of listing. The Committee also considered that the submission's price-volume agreement (PVA) caps were unacceptably high and inadequate to provide budget certainty.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing zolbetuximab, in combination with chemotherapy, on the MOH List of Subsidised Drugs for untreated HER2-negative, CLDN18.2-positive, unresectable advanced gastric or GEJ adenocarcinoma. The decision was based on the unfavourable cost effectiveness of zolbetuximab plus chemotherapy compared with alternative treatments, and the unacceptable PVA proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Approved clinical indication	Subsidy class	Eligible for MediShield Life claims (implementation date)
Zolbetuximab powder for concentrate for solution for infusion (100 mg vial)	Zolbetuximab in combination with fluoropyrimidine and platinum-based chemotherapy for untreated locally advanced unresectable or metastatic HER2-negative and Claudin 18.2-positive gastric or gastroesophageal junction adenocarcinoma.	Not recommended for subsidy	Yes[1] (1 Sep 2026)

[1]Please refer to MOH's website for the MediShield Life claim limit starting from the implementation date.

VERSION HISTORY

Guidance on zolbetuximab for untreated HER2-negative, claudin-18.2-positive, unresectable advanced gastric or gastroesophageal junction adenocarcinoma

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 6 Feb 2026

2. **Guidance updated to reflect that zolbetuximab is eligible for MediShield Life claims**

   Date of Publication 1 Jul 2026