

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1767 - Immunohistochemistry testing for Claudin 18 expression in patients with gastric or gastro-oesophageal junction cancers, to determine eligibility for PBS subsidised zolbetuximab treatment

Applicant: Astellas Pharma Australia Pty Ltd.

Date of MSAC consideration: 3-4 April 2025

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of the application

The integrated codependent application requested:

- Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for the evaluation of Claudin 18.2 (CLDN18.2) expression for the determination of patient eligibility for treatment with zolbetuximab in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required (STREAMLINED) listing of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative G/GOJ adenocarcinoma in patients who have evidence of CLDN18.2 expression.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for immunohistochemistry (IHC) testing for Claudin (CLDN18.2) expression to determine eligibility for zolbetuximab under the Pharmaceutical Benefits Scheme (PBS) in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma. MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its March 2025 meeting was of a mind to recommend zolbetuximab pending a price reduction and other updates. MSAC considered testing would identify patients expected to benefit from zolbetuximab and testing would have no additional safety concerns. MSAC considered the financial impact of testing to the MBS would be relatively low. MSAC considered the proposed fee of \$112 may be high and advised that a fee between \$74.50 to \$112 would be appropriate.

Table 1 MSAC's supported MBS item descriptor

Category 6 – PATHOLOGY SERVICES	Group P5 - Tissue Pathology
MBS item *XXXX Immunohistochemical examination of tumour tissue CLDN18 expression in a patient with locally advanced unresectable or metastatic gastric/gastro-oesophageal junction adenocarcinoma, requested by a specialist or consultant physician, to determine eligibility for a relevant treatment listed under the Pharmaceutical Benefits Scheme (PBS). (See para PN.1.2 of explanatory notes to this category)	
Fee: \$112.00 Benefit: 75% = \$84.00 85% = \$95.20	

Consumer summary
<p>This application from Astellas Pharma Australia Pty Ltd requested Medicare Benefits Schedule (MBS) listing of a test to detect a protein called Claudin 18 in patients with a certain type of stomach or oesophagus cancer called gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma. People who test positive for the protein Claudin 18 (that is Claudin 18 levels that are above a certain threshold) will then be eligible to access a medicine called zolbetuximab, in combination with chemotherapy, under the Pharmaceutical Benefits Scheme (PBS). At the time that this application was made, zolbetuximab was not listed on the PBS, so a codependent application that proposed public funding for zolbetuximab by the Pharmaceutical Benefits Advisory Committee (PBAC) was submitted at the same time.</p> <p>G/GOJ cancer starts in the lining of the stomach and the area where the stomach connects to the oesophagus (gullet). As gastric cancer and gastro-oesophageal cancer are similar in how they develop and behave, patients with gastric cancer and gastro-oesophageal cancer are usually treated in the same way at each stage. G/GOJ cancers tend to be aggressive with poor prognosis/outlook. The 5-year survival rate is about 37% for all stages of the disease combined. Survival is worse for patients with G/GOJ cancer due to a lack of treatments that can specifically target these cancers.</p> <p>A protein called Claudin 18.2 can be found on the surface of some G/GOJ cancer cells. The levels of Claudin 18.2 protein can be tested. A test result is considered positive when the level of Claudin 18 (expression) is above a certain level (threshold). The medicine called zolbetuximab is an antibody that attaches to the Claudin18.2 protein, found on the surface of cancer cells in the stomach. Once attached to cancer cells, zolbetuximab activates the patient's immune system to attack and destroy cancer cells. Zolbetuximab also interferes with</p>

Consumer summary

the structure of cancer cells and the way the cancer cells communicate with each other, which makes it easier for the patient's immune system to destroy them.

MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its March 2025 meeting was of a mind to recommend zolbetuximab to be listed on the PBS provided the cost of the drug was reduced.

MSAC considered Claudin 18 testing was safe and effective and would accurately identify patients expected to benefit from zolbetuximab.

MSAC considered Claudin 18 testing had acceptable value for money and would have a low financial impact. Therefore, MSAC supported listing Claudin 18 testing on the MBS.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported listing Claudin 18 testing on the MBS for people with gastric or gastro-oesophageal cancer. The testing is safe, effective and good value for money. MSAC noted PBAC at its March 2025 meeting was of a mind to recommend the medicine zolbetuximab if the price is reduced, before it is listed on the PBS.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was an integrated codependent application from Astellas Pharma Australia Pty Ltd requesting MBS listing of immunohistochemistry (IHC) testing for Claudin (CLDN18.2) expression in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma, and Pharmaceutical Benefits Scheme (PBS) listing of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with HER2-negative G/GOJ adenocarcinoma and whose tumours are CLDN18.2 positive.

MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its March 2025 was of a mind to recommend zolbetuximab pending a price reduction and other updates including amendments to the proposed restriction criteria and cost of managing zolbetuximab-related adverse events.

MSAC noted the consultation input, which indicated support for this application. MSAC noted public funding would provide equitable access to the new therapies and would ensure people are not required to self-fund therapies. Additionally, MSAC noted feedback which raised that while the proposed medicines offered benefits, patients should be aware of the possible side effects.

MSAC noted the commentary considered that codependence was not supported by counterfactual evidence as the trials evaluating zolbetuximab + chemotherapy exclusively included patients with CLDN18.2+ expression. However, MSAC noted that the Evaluation Sub-Committees (ESCs) considered that the biological plausibility for testing CLDN18.2 expression as a biomarker for targeted treatment with zolbetuximab appeared to be reasonable and aligned with the international guidelines^{1,2}.

MSAC acknowledged that G/GOJ adenocarcinomas are very aggressive malignancies with 5-year

¹ ESMO Gastric Cancer Living Guideline, V1.4 Sept 2024, <https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline/metastatic-disease/metastatic-disease/first-line-her2-negative>

² NCCN Gastric Cancer Guidelines (Version 5.2024), https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

survival rates of approximately 37% for all stages of disease combined and 5-10% for patients with advanced (stage IV) disease. The survival rate is worse for patients with HER2 negative locally advanced unresectable/metastatic G/GOJ carcinomas than those with HER2 positive due to a lack of targeted treatment options for patients with HER2 negative G/GOJ carcinomas. MSAC considered there is a significant unmet need for effective therapies for patients with advanced disease. MSAC noted that CLDN18 testing is not currently funded, but MBS listing of the test would allow access to PBS subsidised zolbetuximab. However, MSAC noted the toxicity profile of zolbetuximab indicated that appropriate mitigation and management of adverse events associated with the treatment would be required.

MSAC noted that the proposed intervention was immunohistochemistry (IHC) testing for CLDN18 expression using the Ventana® CLDN18 (43-14A) RxDx assay, which is the clinical utility standard and was used in the key SPOTLIGHT and GLOW trials. MSAC noted that the Therapeutic Goods Administration (TGA) had made the decision on 2 April 2025 to include the Ventana® CLDN18 (43-14A) RxDx assay as an in vitro diagnostic (IVD) companion test for zolbetuximab treatment on the Australian Register of Therapeutic Goods (ARTG). The comparator was no testing, which MSAC considered to be appropriate. MSAC noted the intervention for the drug was zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy, and the comparator was nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy. MSAC noted that assay antibody 43-14A clone is not isotype-specific, but Claudin 18.2 is the only isotype expressed in gastric tissue. Therefore, MSAC considered that by default the results following testing of gastric tissue using the Ventana® CLDN18 (43-14A) RxDx assay would be reflective of the CLDN18.2 expression level. MSAC noted that intratumor heterogeneity in CLDN18.2 expression exists, but the issue could be addressed by testing multiple biopsies from the same tumour to improve sensitivity. MSAC noted this approach would align with established practices for assessment of gastric cancer biopsies in HER2 testing, where multiple biopsies are routinely assessed. MSAC also noted that CLDN18.2 expression is reported to be highly concordant in matched primary and metastatic tumours. MSAC considered that due to distinguishable membranous staining in tumour cells, interpretation of CLDN18 expression should not be challenging. MSAC also noted that using normal foveolar gastric mucosa as inherent internal control would be helpful in interpretation of CLDN18 expression results.

MSAC noted the applicant's pre-MSAC response that stated that CLDN 18 is not a prognostic factor in G/GOJ patients. MSAC considered that the prognostic impact of CLDN18 testing was not clear from the studies presented in the submission, but also noted that CLDN18.2 expression is reported to be higher in poorly differentiated cells or signet ring cell subtypes, which could explain why CLDN18.2 expression may be associated with a poorer prognosis in some studies.

MSAC noted the proposed MBS item descriptor. MSAC noted that the ESCs agreed with not including a threshold that defined CLDN18 positivity in the MBS item descriptor, but considered that it would be appropriate for the PBS restriction to specify the threshold of $\geq 75\%$ CLDN18.2 expression, in line with the TGA Product Information. MSAC also considered it appropriate that the test be pathologist-determinable to allow parallel HER2 testing.

MSAC noted the high concordance between Ventana® CLDN18 antibody with the Ventana platform and the LSBio antibody with the Dako platform supports the MBS item descriptor to be agnostic to both the IHC platform and the Ventana® CLDN18 antibody.

The proposed fee for CLDN18 testing was \$112. MSAC noted that existing MBS IHC tests for PD-L1 and HER2 have a fee of \$74.50 using similar methodology to CLDN18 testing and most laboratories already have a suitable platform in place for testing. However, MSAC noted that the volume of testing for CLDN18 will be much lower than for PD-L1, as the cancers that involve PD-L1 testing are much more common than G/GOJ cancers, so a fee higher than \$74.50 may be appropriate. Furthermore, taking into account that the cost of the antibody could vary, MSAC concluded that the fee should be between \$74.50 and \$112. MSAC further advised out-of-session that a fee of \$112 was appropriate – as a lower fee than \$112 would be non-viable for laboratories to perform the test.

Regarding comparative safety, MSAC noted that the use of archival samples for parallel testing is recommended to minimise the need for rebiopsy. MSAC agreed with the ESCs consideration that the claim of non-inferior safety compared to no testing was appropriate, due to there being no adverse events related to CLDN18 testing.

MSAC noted that the applicant developed assessment report (ADAR) presented an indirect comparison to inform the data regarding comparative effectiveness of the test and drug combination. SPOTLIGHT and GLOW trials were in patients who were CLDN18-positive, and compared zolbetuximab + chemotherapy with chemotherapy alone. For the comparator of nivolumab + chemotherapy, patients in the CheckMate 649 and ATTRACTION-4 trials were not tested for the biomarker, so their CLDN18 status was unknown. Clinical effectiveness was assessed using a network meta-analysis of these trials. MSAC noted the uncertainty regarding the results of the network meta-analysis as CLDN18 status may be a prognostic factor. On balance, MSAC agreed with the ESCs that the clinical evidence indicated that adding zolbetuximab to standard therapy for CLDN18-positive patients improves survival by 2.2–2.7 months.

MSAC noted the economic evaluation, which was a cost-minimisation approach comparing zolbetuximab in combination with chemotherapy in patients with CLDN18 testing to nivolumab in combination with chemotherapy in patients with no testing, based on the claim of noninferior efficacy and safety. MSAC considered the approach to be appropriate.

MSAC noted the estimated utilisation and revised financial implications using the post-ESC calculated cost-minimised price for zolbetuximab and ESC-supported MBS fee of \$74.50 for CLDN18 testing. MSAC noted the uncertainty in the proportion of patients who would have CLDN18.2 positive tumours due to lack of data on the prevalence of CLDN18.2 positive expression in Australian patients with G/GOJ cancer. MSAC also noted the uncertainty of additional costs to manage infusion related adverse events, and this may underestimate of costs of management. MSAC considered that the financial impact on the MBS was modest. MSAC considered that it was likely that all patients who are biopsied would be tested, so the test uptake rate of **redacted** % used in the financial analysis was appropriate.

MSAC noted and agreed with the need for training and a quality assurance program for pathologists and staff for conducting the test and interpreting the CLDN18 testing results.

4. Background

This integrated codependent application is the first submission for CLDN18 testing for locally advanced unresectable or metastatic G/GOJ adenocarcinoma (hereafter advanced G/GOJ) to the MSAC, and the first submission for zolbetuximab in combination with chemotherapy for advanced G/GOJ adenocarcinoma to the PBAC.

5. Prerequisites to implementation of any funding advice

IHC testing for CLDN18.2 expression is not currently funded, nor available in Australia. The commentary considered that as is the case for other pathology tests, CLDN18 testing involves in vitro diagnostic medical devices (IVD) that require approval by the Therapeutic Goods Administration (TGA) and inclusion on the Australian Register of Therapeutic Goods (ARTG). The submission did not provide any information regarding the TGA/ARTG status of the Ventana® CLDN18 (43-14A) Rx Dx Assay for conducting CLDN18 testing. According to correspondence received from the applicant in March 2024, TGA approval of the Companion Diagnostic (CDx) was anticipated in December 2024.

On 18th October 2024, the US Food and Drug Administration (FDA) approved the Ventana® CLDN18 (43-14A) Rx Dx Assay (Ventana Medical Systems, Inc./Roche Diagnostics) as a

companion diagnostic test to identify patients with G/GOJ adenocarcinoma who may be eligible for treatment with zolbetuximab.³

IHC testing is a well-established technique in all major pathology laboratories and is routinely performed to determine HER2 status in G/GOJ cancer patients. These laboratories are anticipated to have the infrastructure necessary for CLDN18 IHC testing. As the Ventana platform is widely used in Australian laboratories, the Royal College of Pathologists of Australasia (RCPA) noted no major implementation issues (p2, Attachment 12 of the submission). However, it highlighted the importance of specific training for pathologists and staff to accurately perform and interpret the CLDN18 expression test, as well as a Quality Assurance Program (QAP) for conducting the test.

6. Proposal for public funding

A new MBS item was proposed for CLDN18 testing to determine eligibility for zolbetuximab on the PBS, presented in Table 2.

Table 2 Proposed MBS item for CLDN18 expression testing

Category 6 – PATHOLOGY SERVICES
MBS item *XXXX
Immunohistochemical examination of tumour tissue from a patient with locally advanced unresectable or metastatic gastric/gastro-oesophageal junction adenocarcinoma, <i>requested by a specialist or consultant physician</i> , to determine if the requirements relating to CLDN18 expression for access to a relevant treatment listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Fee: \$112.00 Benefit: 75% = \$84.00 85% = \$95.20

Source: Table 1.9, p41 of the submission.

Italics added during the commentary based on the PASC advice (p19, MSAC 1767, Ratified PICO Confirmation, April 2024 PASC meeting).

The proposed MBS item descriptor was consistent with the Ratified PICO Confirmation, except for 'requested by a specialist or consultant physician' which was omitted in the submission. The commentary noted that excluding the requester from the item descriptor would allow any practitioner (e.g., pathologists) to request the CLDN18 test. However, PASC considered that the treating clinician would have the necessary clinical information to determine if CLDN18 testing was required and would be best placed to interpret the results to inform any change in patient management (p19, MSAC 1767 Ratified PICO Confirmation, April 2024 PASC meeting).

The submission also justified that the omission of 'Once per lifetime' from the proposed MBS item descriptor provides flexibility for clinicians to order testing as clinically necessary. The commentary noted, *this* aligned with PASC advice, so was considered reasonable. However, the commentary considered no details were provided as to the rationale or evidence for CLDN18 retesting, and it is not included in the restriction criteria, or factored into the CMA or the financials. Therefore, further information was sought from the sponsor regarding anticipated retesting frequency, estimated uptake and the financial impact.

The submission proposed a fee of \$112 per test, based on analogous IHC tests and all necessary steps required to perform the service, including sample preparation, staining, interpretation by a

³ US food and drug administration, FDA approves zolbetuximab-clzb with chemotherapy for gastric or gastroesophageal junction adenocarcinoma, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zolbetuximab-clzb-chemotherapy-gastric-or-gastroesophageal-junction-adenocarcinoma>, Accessed on 11th Nov 2024.

certified pathologist, and quality control measures. Notably, PASC considered the process for conducting the CLDN18 test to be similar to that of HER2 and PD-L1 (programmed cell death ligand 1) IHC testing (p19, MSAC 1767 Ratified PICO Confirmation, April 2024 PASC meeting). The commentary noted that the newly proposed MBS item fee of \$112 was lower than the previously proposed item fee of \$550; however, it remains higher than the fees for comparable MBS items: \$59.60 for generic IHC examination (MBS item 72846) and \$74.50 for IHC testing to determine HER2 (MBS item 72848) or PD-L1 status (MBS item 72814). The submission stated that the proposed fee structure aligns with the clinical utility of CLDN18 testing in patients with advanced G/GOJ adenocarcinoma; however, the commentary noted no additional clarification was provided to justify a higher fee compared to similar MBS items.

Based on the Ratified PICO Confirmation, it was proposed that CLDN18 testing is eligible to be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS (p17, MSAC 1767 Ratified PICO Confirmation, April 2024 PASC meeting).

Table 3 Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma. Drug: Patients with locally advanced unresectable or metastatic <i>HER2-negative</i> G/GOJ adenocarcinoma who are found positive after Claudin 18 testing (CLDN18.2+).
Intervention	Test: Immunohistochemistry (IHC) testing for CLDN18.2 expression using the Ventana® CLDN18 (43-14A) RxDx Assay Drug: Zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy
Comparator	Test: No testing Drug: For patients without prior immune checkpoint inhibitor (CPI) therapy, nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy. For patients who received nivolumab therapy for Stage II/III disease and subsequently relapsed with locally advanced unresectable or metastatic disease, chemotherapy alone appeared to be the appropriate comparator (<i>as per MSAC 1767 Ratified PICO Confirmation, April 2024 PASC Meeting</i>).
Outcomes	Test-related outcomes: <ul style="list-style-type: none"> • Safety: Adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing. • Diagnostic performance: Sensitivity, specificity, assessment of extent of and implications of discordances between Australian IHC testing and clinical utility standard, test-retest reliability, evidence of stability of proteins in archival tissue, evidence of stability in CLDN18.2 status over time, test failure rate, heterogeneity within tissue samples. • Clinical validity: Positive and negative predictive values, positive and negative likelihood ratios. • Clinical utility of the test: Determine whether testing for CLDN18.2 predicts variation in the treatment effect of zolbetuximab in terms of health outcomes for patients. Drug-related outcomes: <ul style="list-style-type: none"> • Safety: Safety and tolerability of treatment with zolbetuximab compared to alternative treatments assessed by adverse events, physical examination, laboratory findings and vital signs. • Clinical effectiveness outcomes: <ul style="list-style-type: none"> ○ Objective response rate (ORR) ○ Overall survival (OS) ○ Progression-free survival (PFS) ○ Partial response (PR) ○ Complete response (CR) ○ Health-related quality of life (HRQoL) • Healthcare system outcomes: <ul style="list-style-type: none"> ○ Cost of testing per patient and cost of associated re-biopsies (e.g.: early-stage disease that has relapsed, test failure, inadequate sampling) ○ Cost of treatment and cost of treating adverse events ○ Financial implications: number of patients tested; number of patients treated.
Clinical utility standard	Ventana® CLDN18 (43-14A) RxDx Assay Test used in key clinical trials, SPOTLIGHT and GLOW
Clinical claim	In patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma with CLDN18.2+ tumours identified by the IHC testing for CLDN18.2 expression, zolbetuximab in combination with chemotherapy is noninferior compared to nivolumab in combination chemotherapy and no testing in terms of efficacy, with a different but manageable safety profile

Source: Table 1-1, pp25-26 of the submission.

CLDN18 = Claudin 18; G/GOJ = gastric or gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = Immunohistochemistry.

Italics added during evaluation based on the Table 1, p2 of the MSAC 1767 Ratified PICO Confirmation, April 2024 PASC Meeting.

7. Population

The population eligible for CLDN18 testing includes all patients with advanced G/GOJ adenocarcinoma who are treatment naïve for this disease stage. This was confirmed by the

PASC, based on the applicant's pre-PASC response to define one single population diagnosed with advanced disease, of which a subset of patients will have received nivolumab as adjuvant therapy for Stage II/III disease, which has subsequently relapsed into unresectable or metastatic disease (p5, MSAC 1767 Ratified PICO Confirmation, April 2024 PASC meeting). The commentary noted a discrepancy in the test population and the requested restriction for zolbetuximab. The commentary considered that the requested restriction for zolbetuximab was broader than the inclusion criteria of the key clinical trials of zolbetuximab (i.e., SPOTLIGHT and GLOW), as it included patients with oesophageal adenocarcinoma in addition to those with G/GOJ adenocarcinoma. In contrast, the clinical trials only enrolled patients with G/GOJ adenocarcinoma. Furthermore, the requested restriction was not aligned with the proposed TGA indication for zolbetuximab as the first-line treatment for patients with advanced G/GOJ.

The proposed biomarker test in the submission was for both the isoforms of CLDN18 (CLDN18.1 and CLDN18.2). CLDN18.1 is primarily expressed in lung tissue, while CLDN18.2 is primarily expressed in gastric tissue. In normal tissue, CLDN18.2 is located in tight junctions forming a paracellular barrier in gastric mucosa cells to control the flow of molecules between cells; however, during malignant transformation, the loss of cell polarity exposes the epitope of CLDN18.2, making it more accessible to antibodies. Therefore, when the CLDN18 biomarker test is conducted in gastric tissue, it primarily reflects CLDN18.2, as CLDN18.1 is rarely present in gastric tissues.

Proposed testing using the Ventana CLDN18 (43-14A) RxDx does not specifically target specific isoforms of CLDN18 but recognises the C-terminus of CLDN18 only. Therefore, both CLDN18.1 (mainly expressed in lung tissue) and CLDN18.2 (mainly expressed in gastric tissue) are detected. The applicant stated that CLDN18.1 is minimally expressed in gastric tissue and therefore tests of gastric tissue using Ventana CLDN18 (43-14A) RxDx will give an estimation of the CLDN18.2 level. It is unclear to what extent CLDN18.1 is expressed in gastric tissue and therefore it is possible that the CLDN18.2 level could be overestimated when using the Ventana CLDN18 (43-14A) RxDx test. This has implications for the effectiveness of zolbetuximab, which has been demonstrated in the FAST trial to have a survival benefit only in patients who have CLDN18.2 expression detected in $\geq 70\%$ of tumour cells. It is unclear whether other IHC CLDN18 tests (e.g. Novus and LSBio) specifically target CLDN18.2.

Zolbetuximab is a genetically engineered, highly purified chimeric (mouse/human immunoglobulin G1 [IgG1]) monoclonal antibody targeted against CLDN18.2. Upon binding, zolbetuximab induces cancer cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

The commentary considered the biological rationale for testing for CLDN18.2 expression as a biomarker for targeted treatment with zolbetuximab to be reasonable.

Gastric cancer (GC) originates in the stomach lining, while GOJ cancer develops in the area between the stomach and the oesophagus. In patients with G/GOJ cancer, the prevalence of CLDN18.2+ (defined as $\geq 75\%$ of tumour cells showing moderate-to-strong membranous staining above background) is 38.38%. This was based on a weighted proportion of patients from SPOTLIGHT (38.37%) and GLOW (38.40%) trials whose tumours were CLDN18.2+ expression. Based on the threshold of $\geq 75\%$, the prevalence of CLDN18.2 positivity was reported in 24% of

the Italian population⁴, 33.4% of the Japanese population⁵, and 44.4% of the U.S. population⁶ in retrospective studies. An independent search conducted during the commentary found no data on the prevalence of CLDN18.2+ in Australian cases of G/GOJ cancers. As a result, the commentary considered that there is uncertainty about the proportion of patients with CLDN18.2+ expression in Australia.

In the current clinical management algorithm presented in the submission, patients with advanced or metastatic G/GOJ adenocarcinoma receive a combination of fluoropyrimidine- and platinum-containing chemotherapy. Notably, HER2 testing is done as part of the standard work up for G/GOJ cancer diagnosis and staging. For patients with HER2-positive tumours, trastuzumab is added to chemotherapy. For patients with HER2-negative tumours, nivolumab is added to chemotherapy (hereafter nivolumab + chemotherapy). For the subgroup of the population with HER2-negative tumours who have relapsed after early-stage disease treatment with nivolumab or have contraindications to PD-L1 inhibitors, chemotherapy alone appears to be the most appropriate therapy. In the proposed clinical management algorithm, CLDN18 testing is to be performed in parallel with HER2 testing in all patients with advanced or metastatic G/GOJ adenocarcinoma. This was in line with the PASC advice, given that parallel testing may facilitate timely treatment decisions (p5, MSAC Application 1767 Ratified PICO Confirmation, April 2024 PASC Meeting). Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy (hereafter zolbetuximab + chemotherapy), is proposed as a novel first-line treatment for patients with advanced G/GOJ adenocarcinoma whose tumours are HER2-negative and CLDN18.2+. The submission was consistent with the Ratified PICO Confirmation regarding the population to be tested and treated. However, the requested restriction for zolbetuximab, which specifies that 'patient must be untreated (up until initiating this drug) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer', does not align with the treatment population outlined in the Ratified PICO Confirmation. See Section 3 of the Economics Sub Committees: Advice to PBAC for more details.

8. Comparator

The proposed comparator is no testing for CLDN18.2 expression, as testing for CLDN18.2 expression is not currently funded in Australia. The submission nominated nivolumab + chemotherapy as the main comparator for the zolbetuximab + chemotherapy. For patients who received nivolumab therapy following early-stage disease treatment and subsequently relapsed or have contraindications to PD-1/PD-L1 inhibitors, chemotherapy alone was the comparator. The commentary considered the choice of comparator for both the test and the drug to be appropriate and aligned with the Ratified PICO confirmation.

9. Summary of public consultation input

Consultation input was received from two medical, health, or other (non-consumer) organisations, and one consumer organisation.

⁴ Pellino, A., et al., (2021), 'Association of CLDN18 Protein Expression with Clinicopathological Features and Prognosis in Advanced Gastric and Gastroesophageal Junction Adenocarcinomas', *J Pers Med*, 11(11):1095, <https://pubmed.ncbi.nlm.nih.gov/34834447/>

⁵ Kubota, Y., et al., (2023), 'Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer', *ESMO Open*, <https://doi.org/10.1016/j.esmoop.2022.100762>

⁶ Waters, R., et al., (2024), 'Retrospective Study of Claudin 18 Isoform 2 Prevalence and Prognostic Association in Gastric and Gastroesophageal Junction Adenocarcinoma', *JCO Precision Oncology*, 8, <https://ascopubs.org/doi/10.1200/PO.23.00543>

The organisations that submitted input were:

- Australian Pathology
- The Royal College of Pathologists of Australasia (RCPA)
- PanCare Foundation

Level of support for public funding

All organisations expressed support for the public funding of this service.

Comments on PICO

Both Australian Pathology and RCPA noted their agreement with the proposed PICO.

Perceived Advantages

Pancare Foundation noted the following advantages with the proposed service:

- Facilitating improved progression free survival and overall survival.
- Reduced financial burdens.
- Increased sense of hope.

Support for Implementation /issues

- RCPA noted that all semiquantitative IHC assays that are used to determine access to a specific drug have a higher level of validation requirements, and therefore noted the need for adequate pathologist training and ongoing QC/QA to ensure they are being performed correctly.
- RCPA also noted that if labs are using the IHC antibody as an IVD test (lab-developed test), the requirements for assay validation are more stringent and costly than those of diagnostic antibodies.

10. Characteristics of the evidence base

The approach taken in the submission was to present linked evidence to support the contention that targeting CLDN18.2 expression with zolbetuximab + chemotherapy produced noninferior clinical outcomes to no testing for CLDN18.2 expression and nivolumab + chemotherapy. Table 4 summarises the linked evidence presented in the submission.

Table 4 Summary of the linked evidence approach

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Used in modelled evaluation
Accuracy and performance of the test (cross-sectional accuracy)	Concordance with clinical utility standard (Jasani et al., 2024). Analytical performance and reproducibility of Ventana® CLDN18 (43-14A) RxDx IHC assay (Stratton et al., 2023)	<input checked="" type="checkbox"/> k=1 n=15 ^a <input checked="" type="checkbox"/> k=1 n=NR ^b	Risk of bias assessment was not provided in the submission. <i>The commentary considered that Jasani et al., 2024 was at risk of bias and Stratton et al., 2023 was at high risk of bias, based on QUADAS-2 assessment.</i>	No
Prognostic evidence (longitudinal accuracy)	Comparison of health outcomes in patients receiving usual care (chemotherapy), conditional on the presence or absence of biomarker-positive status (Kubota et al., 2023; Pellino et al., 2021; Waters et al., 2024)	<input checked="" type="checkbox"/> k=3 n=1,058 ^c	Risk of bias assessment was not provided in the submission. <i>The commentary considered that all three retrospective studies were at moderate risk of bias, based on QUIPS risk of bias tool.</i>	No
Change in patient management	Not explicitly assessed. Patients tested positive for CLDN18.2 expression would be eligible for treatment with zolbetuximab.	<input type="checkbox"/> k=0 n=0	-	-
Health outcomes (clinical utility)	As per treatment effect (enriched).	<input checked="" type="checkbox"/> k=2 n=1,072	Low	Yes
Predictive effect (treatment effect variation)	No evidence presented.	<input type="checkbox"/> k=0 n=0	-	-
Treatment effect (enriched)	Two RCTs with all patients who have tested positive for CLDN18.2, randomised to either zolbetuximab + chemotherapy, or chemotherapy alone.	<input checked="" type="checkbox"/> k=2 n=1,072	Low	Yes

Source: Table 2-6, pp57-58; Table 2-13, p78; Table 2-14, p78; Table 2-15, p78 of the submission.

CLDN18.2 = claudin 18.2; IHC = immunohistochemistry; k=number of studies; n = number of patients; NR = not reported; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies; QUIPS = Quality in Prognostic Studies; RCT = randomised controlled trial.

^a 15 resection samples were used to construct tissue microarray (Jasani et al., 2024).

^b 24 tissue cases were stained for repeatability analysis; 100 tissue cases were evaluated for inter- and intra-reader precision; and 28 tissue cases were stained for interlaboratory reproducibility tests (Stratton et al., 2023).

^c Calculated based on n=408 in Kubota et al., 2023; n=350 in Pellino et al., 2021; n=300 in Waters et al., 2024.

Italics added during the evaluation.

11. Comparative safety

Adverse events from testing

The CLDN18 test is expected to be performed on the same tumour specimens used for histological assessment and the standard diagnostic work-up in the management of advanced or metastatic G/GOJ cancers. CLDN18 testing could also be performed on archival tissue for those who progress from earlier stages of G/GOJ cancer. As a result, no additional adverse events (AEs) are expected from testing.

In line with the post-PASC advice, the commentary noted that the submission did not present AEs associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing. PASC

confirmed that most patients are expected to undergo parallel testing of HER2 and CLDN18, and the re-biopsy rate was likely to be small and insignificant (p12, MSAC 1767 Ratified PICO Confirmation, April 2024 meeting).

Adverse events from changes in management

The use of CLDN18 testing would result in the majority of those with CLDN18.2+ expression receiving zolbetuximab + chemotherapy. No formal indirect comparisons were conducted in the submission to determine the relative safety of zolbetuximab and nivolumab, in combination with chemotherapy.

Based on unanchored and unadjusted indirect treatment comparison of the pooled safety data from zolbetuximab trials (SPOTLIGHT and GLOW) and the nivolumab trial (CheckMate 649), a higher proportion of Grade 3-4 treatment-emergent AEs (TEAEs) occurred in active treatment arms; 70.9% vs 63.4% in zolbetuximab arm compared to chemotherapy arm (risk difference [RD]: 0.08; 95% Confidence Interval [CI]: 0.03, 0.12) and 69.1% vs 59.5% in nivolumab arm compared to the chemotherapy arm (RD: 0.10; 95% CI: 0.05, 0.14), with no notable difference between zolbetuximab and nivolumab arms (RD: 0.02; 95% CI: -0.03, 0.69). This trend was also observed for treatment related Grade 3-4 TEAEs (RD: 0.07; 95% CI: 0.02, 0.12). The rate of serious TEAEs were similar between zolbetuximab and chemotherapy arms (46% vs 46.5%; RD: -0.01; 95% CI: -0.05, 0.04), while a higher proportion of patients experienced serious TEAEs in the nivolumab arm compared to chemotherapy arm (54.1% vs 43.7%; RD: 0.10; 95% CI: 0.05, 0.15). Treatment-related serious TEAEs were more frequent in zolbetuximab arm (25.1% vs 18.4%; RD: 0.07; 95% CI: 0.01, 0.08) and nivolumab arm (22.0% vs 12.1%; RD: 0.10; 95% CI: 0.06, 0.14) than in the respective chemotherapy arm, with no notable difference in magnitude between zolbetuximab and nivolumab arms (RD: 0.03; 95% CI: -0.02, 0.08). More patients in nivolumab arm (36.3%) compared to zolbetuximab arm (20.6%) discontinued treatment due to TEAEs (RD: -0.16; 95% CI: -0.21, -0.11).

Notably, zolbetuximab and nivolumab have distinct safety profiles. The most common Grade 3-4 TEAEs with zolbetuximab were nausea (11.6%), vomiting (12.8%), neutropenia (9.9%) and decreased appetite (4.7%), whereas neutropenia (defined as absolute neutrophil count <1500 per microliter; 15.7%), neutrophil count decreased (10.7%), anaemia (6.0%), lipase increases (5.8%) were the most common Grade 3-4 TEAEs reported for nivolumab.

The commentary noted that it was difficult to assess the comparative safety due to the unanchored indirect nature of the comparison and the distinct safety profiles between zolbetuximab and nivolumab.

12. Comparative effectiveness

A summary of the data used to inform the comparisons of test and drug combinations is presented in Table 5.

Table 5 Data availability to inform comparisons

Proposed test vs no test	No evidence presented		
Proposed test vs alternative test	Global Ring Study by Jasani et al. (2024) compared Ventana® CLDN18 (43-14A) RxDx IHC assay to Novus and LSBio antibodies, stained on Ventana, Dako and Leica platforms		
	Proposed drug	Comparator drug	
	Zolbetuximab + chemotherapy	Chemotherapy	Nivolumab + chemotherapy
Biomarker test positive	SPOTLIGHT and GLOW trials	SPOTLIGHT and GLOW trials	CheckMate 649 and ATTRACTION-4; however, the biomarker was not tested in these trials and the study participants' CLDN18 status was unknown.
Biomarker test negative	No evidence presented	No evidence presented	

Source: Compiled during evaluation.

CLDN18 = Claudin 18; IHC = immunohistochemistry.

The evidence presented to show concordance between the clinical utility standard (Ventana® CLDN18 (43-14A) RxDx Assay) and IHC CLDN18 testing, was limited to one study (Jasani et al., 2024)⁷, which has potential bias in the flow and timing domain, as evaluated by the commentary. Similarly, the evidence supporting analytical performance and reproducibility was based on a poster presentation (Stratton et al., 2023)⁸, which was considered to have a high risk of bias by the commentary due to incomplete information. The evidence presented for clinical effectiveness was based on an indirect comparison of zolbetuximab + chemotherapy (SPOTLIGHT and GLOW trials) and nivolumab + chemotherapy (CheckMate 649 and ATTRACTION-4) via network-meta-analysis (NMA). While the trials were at low risk of bias, the commentary regarded the results of the NMA to be uncertain due to transitivity issues between the trials, including differences in eligibility criteria, primary disease site, ancestry, follow-up duration, and subsequent anti-cancer therapies.

However, as outlined in Table 5, the commentary considered not all parts of the analytic framework were addressed. The commentary noted that no evidence comparing the outcomes of CLDN18 testing versus no testing was presented. Additionally, the trials evaluating zolbetuximab + chemotherapy exclusively included patients with CLDN18.2+ expression, whereas CLDN18.2 expression status was not assessed in the nivolumab + chemotherapy trials. The ESCs suggested that summarising the results of the early studies of zolbetuximab showing no effect in patients with CLDN18.2- expression would support the claim that this biomarker has a predictive effect on the effectiveness of zolbetuximab.

The commentary noted that the populations, tests and treatment regimens were not always transferrable across the evidence linkages, as they varied considerably.

Comparative accuracy/test performance

The proposed test is IHC testing for CLDN18. The Ventana® CLDN18 (43-14A) RxDx Assay used in the key trials (i.e., SPOTLIGHT and GLOW) represented the clinical utility standard.

Jasani et al. (2024) assessed the analytical reproducibility and comparability of IHC testing for CLDN18, of which the inter-laboratory concordance was evaluated using three CLDN18 antibodies (Ventana, LSBio, and Novus) stained on three IHC-staining platforms (Ventana

⁷ Jasani B., et al (2024); 'CLDN Study Group; Dodson A. Global Ring Study to Investigate the Comparability of Total Assay Performance of Commercial Claudin 18 Antibodies for Evaluation in Gastric Cancer', *Lab Invest*;104(1):100284.

⁸ Stratton, S., et al., (2023), 'Analytical and Clinical Performance of the VENTANA CLDN18 (43-14A) RxDx Assay in Gastric and Gastroesophageal Junction Adenocarcinoma Tissue Samples for Patient Identification in Two Phase 3 Trials of Zolbetuximab', Poster: <https://medically.roche.com/content/dam/pdmahub/restricted/oncology/ecp-2023/ECP-2023-poster-stratton-analytical-and-clinical-performance-of-the-VENTANA-CLDN18.pdf>

BenchMark, Dako Autostainer Link 48, and Leica Bond). Notably, the LSBio and Novus antibodies were stained on all three platforms, whereas Ventana antibody was analysed only on the Ventana platform. Table 6 presents a summary of the concordance results for CLDN18 testing, comparing the combined performance of different assays and platforms against the clinical utility standard, as calculated by the commentary.

Table 6 Concordance results of IHC CLDN18 testing compared with the clinical utility standard

Antibody	IHC-staining platforms	PPA (%)	NPA (%)	OPA (%)
Ventana® CLDN18 (43-14A) RxDx IHC	Ventana	84.4	94.6	89.8
Novus	Ventana	55.3	94.6	74.2
	Dako	60.5	90.4	75.5
	Leica	71.5	87.6	79.6
LSBio	Ventana	86.5	82.8	84.6
	Dako	91.0	93.2	92.1
	Leica	85.3	86.5	85.9

Source: Calculated using evaluation using Table 2-12, p77 of the submission.

CLDN18 = Claudin 18; IHC = immunohistochemistry; PPA = positive percent agreement; NPA = negative percent agreement; OPA = overall percent agreement.

Italics calculated during evaluation.

Based on the Principles of Analytic Validation of Immunohistochemical Assays: Guideline Update by the College of American Pathologists, an overall concordance (represented by Overall Percent Agreement [OPA]) of at least 90% should be achieved between a new assay and a comparator assay.⁹ The Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) for the Ventana platform with the Ventana® CLDN18 (43-14A) RxDx IHC antibody were 84.4% and 94.6%, respectively, resulting in an OPA of 89.8%. In comparison, the OPA for the Novus antibody was lower across all platforms, ranging from 74% to 80%, demonstrating low consistency. The LSBio antibody performed notably better with the Dako platform (92.1% OPA), compared to its performance on the Ventana and Leica platforms (84.6% and 85.9% OPA, respectively). The commentary noted that both the Ventana® CLDN18.2 (43-14A) RxDx IHC antibody with the Ventana platform and the LSBio antibody with the Dako platform demonstrated excellent levels of concordance. In contrast, the Novus antibody showed lower consistency and reliability across the different platforms used.

Additionally, Stratton et al. (2023) presented data showing the robustness of analytical and clinical performance of the Ventana® CLDN18 (43-14A) RxDx IHC in G/GOJ adenocarcinoma with high degree of reproducibility in terms of variation in reagent lot, instrument, day, site, and reader. However, the commentary noted that the study was available as a poster only, with limited data on inclusion criteria and missing data.

The commentary noted that the submission did not present a comparison of the analytical performance between the Ventana® CLDN18 (43-14A) RxDx Assay (the clinical utility standard) and other IHC platform and CLDN18 antibody combinations in the Australian setting. Furthermore, feedback from the March 2024 meeting with the Royal College of Pathologists of Australasia (RCPA) indicated that Australian laboratories are unlikely to set up an in-house CLDN18 test due to the associated costs, the time required for validation, and the expected low demand for the test (p2, Attachment 12 of the submission). PASC confirmed that Ventana is the most common IHC platform used in Australia, noting that there are other relevant IHC platforms and CLDN18 antibodies available. However, none of the CLDN18 antibodies were TGA registered at the time of evaluation. The commentary noted that the high concordance between Ventana®

⁹ Goldsmith, J., et al., (2024), 'Principles of Analytic Validation of Immunohistochemical Assays: Guideline Update', *Arch Pathol Lab Med*, 148 (6): e111–e153, <https://doi.org/10.5858/arpa.2023-0483-CP>

CLDN18 antibody with the Ventana platform and the LSBio antibody with the Dako platform supports the MBS item descriptor to be agnostic to both the IHC platform and the CLDN18 antibody, noting the low concordance observed across all IHC platform with the Novus antibody.

The submission found no stability data specific to CLDN18 in stored formalin-fixed paraffin-embedded (FFPE) samples during the literature search. However, Jasani et al. (2024) conducted a stability sub study in which tissue microarray (TMA) sections were stored for three months at room temperature and the recommended temperature of 4 °C prior to IHC staining and scoring. That study reported no staining differences compared to the original slides across various antibody and platform combinations, except for Novus on Leica, which showed weaker staining after three months. Additionally, the submission suggested that CLDN18.2 antigenicity could be preserved for up to a year, based on Jasani et al. (2024), who reported minimal antigenicity loss in various antigens in FFPE blocks and TMAs. However, the commentary deemed this uncertain as the stability evidence was based on short term storage of the TMA and there was lack of specific evidence for longer duration of sample storage.

The submission presented findings from three studies evaluating stability of CLDN18.2 positivity over time: Shitara et al. (2023)¹⁰, Kubota et al. (2023), and Pellino et al. (2021). The commentary noted two additional studies reporting concordance between primary and metastatic tissue: Waters et al. (2024) and Coati et al. (2019)¹¹.

- Shitara et al. (2024) reported a low concordance rate of 61.1% between the archive and baseline tumour tissue samples, with the median time between collection of samples of more than one year.
- Kubota et al. (2023) observed a concordance rate of 75.1% before and after first-line chemotherapy.
- Pellino et al. (2021) reported a 66.7% concordance rate between biopsy and surgical samples and an 81.5% concordance rate between primary and metastatic tissue.
- Waters et al. (2024) reported a concordance rate of 73.0%, while Coati et al. (2019) reported 86.7% between primary and metastatic tissue.

The commentary noted that the stability of CLDN18.2 status over time was not high, potentially influenced by factors such as prior therapies, intertumoral heterogeneity between primary and metastatic sites, and differences between archival and baseline samples from the same tumour, as reported by Shitara et al. (2024). Nonetheless, the commentary acknowledged some evidence supporting concordance of CLDN18.2 expression between primary and metastatic samples.

The submission presented findings from four studies evaluating heterogeneity within tissue samples (Coati et al., 2019; Pellino et al., 2021; Kim et al., 2023¹²; and Angerilli et al., 2024¹³). Coati et al. (2019) found intratumoral variability in CLDN18 expression in 40.3% of GCs and 33.6% of GOJ cancers, with 28.8% of metastatic samples showing heterogeneous CLDN18 status. Kim et al. (2023) reported heterogeneous CLDN18.2 expression in 31% of patients with Stage I-III resectable GC, likely due to discrepancies between endoscopic biopsies and surgical

¹⁰ Shitara, K., et al., (2024), 'Global prevalence of claudin 18 isoform 2 in tumours of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma', *Gastric Cancer*, 27(5):1058-1068. <https://link.springer.com/article/10.1007/s10120-024-01518-1>

¹¹ Coati, I., et al., (2019), 'Claudin-18 expression in esophagogastric adenocarcinomas: a tissue microarray study of 523 molecularly profiled cases', *Br J Cancer*, 121, 257–263, <https://doi.org/10.1038/s41416-019-0508-4>

¹² Kim, S., et al., (2023), 'Clinicopathologic features and prognostic value of claudin 18.2 overexpression in patients with resectable gastric cancer', *Sci Rep*, 13:20047, <https://doi.org/10.1038/s41598-023-47178-6>

¹³ Angerilli V., et al., (2024), 'Claudin-18.2 testing and its impact in the therapeutic management of patients with gastric and gastroesophageal adenocarcinomas: A literature review with expert opinion', *Pathol Res Pract*, 254:155145, <https://www.sciencedirect.com/science/article/pii/S0344033824000566?via%3Dihub>

specimens, with greater heterogeneity observed in CLDN18.2- cases. Pellino et al. (2021) investigated CLDN18 intratumor heterogeneity in 93 surgically treated cases (77 GC cases and 16 GOJ cases). Sensitivity increased from two to nine biopsies (93-100%), with stable specificity between six to eight biopsies (98.5-98.9%). Angerilli et al. (2024) noted that CLDN18.2 staining exhibits a high degree of spatial intratumoral heterogeneity, similar to HER2 which should be assessed using surgical samples or, at a minimum, six biopsy samples representative of the neoplastic lesion, including both primary and metastatic sites.

Prognostic evidence

Based on the literature search, the submission identified ten studies evaluating the prognostic value of CLDN18.2 expression, and additionally found one review (Mathias-Machado et al., 2024¹⁴), one meta-analysis (Ungureanu et al., 2021¹⁵), and two studies (Water et al., 2024 and Sanada et al., 2006¹⁶). An independent search conducted during the commentary identified a recently published systematic review and meta-analysis (Moraes et al., 2024)¹⁷.

Table 7 presents the summary of studies evaluating the prognostic effect of CLDN18.2 in G/GOJ cancers.

¹⁴ Mathias-Machado, M., et al., (2024), 'Claudin 18.2 as a New Biomarker in Gastric Cancer—What Should We Know?', *Cancers*, 16(3):679. <https://doi.org/10.3390/cancers16030679>

¹⁵ Ungureanu, B., et al., (2021), 'Clinicopathologic Relevance of Claudin 18.2 Expression in Gastric Cancer: A Meta-Analysis.' *Front Oncol*, 11:643872, <https://pubmed.ncbi.nlm.nih.gov/33747967/>

¹⁶ Sanada, Y., et al., (2006), 'Down-regulation of the claudin-18 gene, identified through serial analysis of gene expression data analysis, in gastric cancer with an intestinal phenotype', *J Pathol*, 208(5):633-42, <https://pubmed.ncbi.nlm.nih.gov/16435283/>

¹⁷ Moraes FCA., et al., (2024), 'The role of CLDN18.2 in gastric cancer prognosis: a systematic review and meta-analysis', *Biomarkers*, 29(8):528-538

Table 7 Studies evaluating the prognostic effect of CLDN18.2 in G/GOJ cancers

Study	Type of study	Country	N	Definition of CLDN18.2 positivity	Frequency	OS impact (p-value)
Studies identified in the literature search						
Arnold et al. (2020) ^a	Retrospective	Germany	414	Immunoreactivity score (IRS) > 8	17.1%	p=0.94
Dottermusch et al. (2019) ^a	Retrospective	Germany	481	Positive histoscore (H-score)	42.2%	p=0.44
Hong et al. (2020)	Prospective	Republic of Korea	430 ^b	>5%	14.1%	P=0.10
Kayikcioglu et al. (2023)	Retrospective	Turkey	65	Any positive staining	73.8%	p=0.09
Kim et al. (2020)	Retrospective	Republic of Korea	77 ^c	High expressor by H-score (median) >45	n/a	p=0.15
Liu et al. (2024)	Retrospective	China	185	High H-score >40	60.5%	p<0.05
Moentenich et al. (2020) ^a	Retrospective	Germany	385	Positive H-score	18.4%	p=0.52
Pellino et al., (2021)	Retrospective	Italy	350	>75%	33.4%	p=0.93
Wang et al., (2023)	Retrospective	China	451	Positive H-score	54.3%	p=0.03^c
Xu et al., (2020)	Retrospective	China	105	Moderate-strong >40% / >90% of cells	64.8% / 21.0%	p=0.13 / p=0.82
Studies included in the review by Mathias-Machado et al. (2024)^d						
Zhu et al. (2013)	Retrospective	China	329	Immunoreactivity score (IS > 4)	53.2%	p = 0.47
Baek et al. (2019)	Retrospective	Republic of Korea	367	>50%	29.4%	p = 0.91
Kubota et al. (2023)	Retrospective	Japan	408	>75%	24%	p = 0.19
Resnick et al. (2005)	Retrospective	United States	146	>2+	-	p = 0.01
Jung et al. (2011)	Retrospective	Republic of Korea	72	>25%	44.4-73.6%	p = 0.05
Jun et al. (2014)	Retrospective	Republic of Korea	134	>10%	25.5-29.9%	p = 0.01
Kohmoto et al. (2020)	Retrospective	Japan	394	High mRNA expression	18%	p = 0.001
Studies identified in additional literature search						
Waters et al. (2024)	Retrospective	United States	304	≥50% / ≥75%	56.3% / 44.4%	NR ^e
Sanada et al. (2006)	Retrospective	Republic of Korea	367	Not down-regulated by H-score >50	29.4%	p = 0.91
Meta-analysis						
Ungureanu et al. (2021)	Three studies (Dottermusch et al., 2019; Moentenich et al., 2020; Arnold et al., 2020) were included in the meta-analysis of the hazard ratio for OS for patients who were CLDN18.2+ vs CLDN18.2-					p = 0.95

Source: Table 2-7, pp60-61; Table 2-8, p64; and Figure 2-3, p62 of the submission.

CLDN18.2 = Claudin 18.2; N = number of participants; NR = not reported; OS = overall survival.

^a Also included in Ungureanu et al. (2021) meta-analysis.

^b 19.8% (N = 85) gastric cancer.

^c Metastatic diffuse-type gastric cancer.

^d The list of studies does not include those already incorporated in the literature search provided in the submission.

^e HR=0.92 (95%CI: 0.62,1.37) for CLDN18.2+ patients at ≥50% threshold; HR=0.75 (95%CI: 0.50,1.14) for CLDN18.2+ patients at ≥75% threshold

Bold indicates statistical significance.

The definition of CLDN18.2 positivity varied across the studies. Only the following three studies used the same CLDN18.2 positivity threshold of $\geq 75\%$ as in the pivotal trials (i.e., SPOTLIGHT and GLOW):

- Kubota et al. (2023) found no significant differences in overall survival (OS) between CLDN18.2+ and CLDN18.2- patients with advanced G/GOJ cancers (hazard ratio [HR] = 1.26; 95% confidence interval [CI]: 0.89, 1.78), with an absolute difference of 1.7 months favouring CLDN18.2- patients. Progression-free survival (PFS) and overall response rates (ORR) also showed no significant differences according to CLDN18.2 status.
- Pellino et al. (2021) also concluded that CLDN18.2 positivity was not associated with OS in patients with advanced G/GOJ cancers ($p = 0.926$).
- Waters et al. (2024) reported an HR of 0.75 (95% CI: 0.50, 1.14), indicating a 33.3% higher OS in the CLDN18.2- compared to the CLDN18.2+ patients with G/GOJ cancer, however, this was not significant.

While the results from these studies consistently suggest no statistically significant clinical outcomes associated with CLDN18.2 positivity using the $\geq 75\%$ threshold, there was a trend towards improved OS in patients with CLDN18.2- expression. The commentary noted that these studies have limitations, including small sample size, retrospective design, single-institution settings, with no validation cohort. Furthermore, there was heterogeneity in the populations studied in terms of disease stage, treatment, and HER2 status.

The commentary noted that the results from a recent systematic review and meta-analysis (Moraes et al., 2024) demonstrated that CLDN18.2 is a robust negative prognostic indicator for overall survival in gastric cancer patients. The review included 15 studies encompassing 4,085 patients with varying definitions of CLDN18.2 positivity. Patients with CLDN18.2- exhibited a statistically significant trend towards prolonged OS (HR: 1.20; 95% CI: 1.07, 1.34, $k=12$) and non-statistically significant trend towards prolonged PFS (HR: 1.25; 95% CI: 0.98, 1.61, $k=4$) when compared to CLDN18.2+ patients. *Overall, the ESCs concluded that the available evidence suggests that expressing CLDN18.2 is possibly prognostic of poorer health outcomes in gastric cancer, but the quality and applicability of this evidence to the proposed Australian clinical population is uncertain.*

Predictive evidence

No predictive evidence was provided in the submission using the threshold of $\geq 75\%$ (i.e. no clinical evidence was provided showing a differential effect of zolbetuximab in those with and without the biomarker). Notably, the FAST trial, a phase II study of zolbetuximab, presented evidence of efficacy in patients with a lower threshold of $\geq 40\%$ CLDN18.2 expression. In patients with CLDN18.2 expression in $\geq 70\%$ of tumour cells, significant improvement in survival was observed with zolbetuximab + chemotherapy compared to chemotherapy alone. However, for patients with 40%-69% CLDN18.2 expression, there was no significant improvement in survival with zolbetuximab + chemotherapy compared to chemotherapy alone. The improved efficacy among the subgroups of patients with high CLDN18.2 expressing tumours supports a relationship between CLDN18.2 expression and zolbetuximab. In addition, the ESCs suggested that summarising the results of the early studies of zolbetuximab showing no effect in patients with CLDN18.2- expression would further support the claim that this biomarker has a predictive effect on the effectiveness of zolbetuximab.

Change in management in practice

The European Society of Medical Oncology (ESMO) Gastric Cancer Living Guideline recommends zolbetuximab + chemotherapy for patients who have tested positive for CLDN18.2 expression ($\geq 75\%$), HER2-negative, and PD-L1 negative tumours in the first-line metastatic setting. Zolbetuximab is also a potential option for some patients with CLDN18.2+, HER2-negative and

PD-L1 positive tumours (ESMO guidelines). The commentary noted that these recommendations were made despite the lack of evidence about predictive value of CLDN18.2 expression. The submission stated that MBS listing of IHC CLDN18 testing and PBS listing of zolbetuximab will provide an additional treatment option for patients with HER2-negative G/GOJ cancers.

The commentary noted that there is no change in clinical management for HER2-negative G/GOJ cancer patients who do not test positive for CLDN18.2 expression as per the current and proposed clinical management algorithms.

As highlighted in the comparative accuracy section, the sensitivity and specificity of the Ventana® CLDN18 (43-14A) RxDx IHC assay was 84% and 95%, respectively. This indicated that 16% of cases with CLDN18.2 expression may have false negative results, while 5% of non-CLDN18.2 expression may yield false positive results. The commentary considered that while the false negative results may not result in a clinically significant impact if the claim of noninferiority between zolbetuximab and nivolumab, in combination with chemotherapy, is accepted by the PBAC, the treatment of false positive patients with zolbetuximab poses a potential risk. This is because there is no evidence supporting the efficacy and safety of zolbetuximab in patients with CLDN18.2- expression, whereas evidence exists to support the use of nivolumab irrespective of CLDN18.2 expression.

Claim of codependence

Zolbetuximab, a chimeric immunoglobulinG1 (IgG1) monoclonal antibody, binds to CLDN18.2, a tight junction protein that is highly expressed in G/GOJ adenocarcinoma. Upon binding, zolbetuximab induces cancer cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

The CLDN18.2 threshold for a positive result was $\geq 75\%$ tumour cells showing moderate-to-strong membranous staining, while $< 75\%$ indicated a negative result. This $\geq 75\%$ threshold was based on evidence from SPOTLIGHT and GLOW trials. Additionally, this was supported by the FAST study¹⁸, which was a phase II study that included adults with locally advanced, inoperable, recurrent, or metastatic G/GOJ cancers and CLDN18.2+ expression in $\geq 40\%$ of tumour cells. In patients with CLDN18.2 expression in $\geq 70\%$ of tumour cells, significant improvement in PFS and OS was observed with zolbetuximab + chemotherapy compared to chemotherapy alone. However, patients with 40%-69% CLDN18.2 expression did not demonstrate significant differences between the two arms. The authors stated that the improved efficacy among the subgroups of patients with high CLDN18.2 expressing tumours support a relationship between CLDN18.2 expression and zolbetuximab. In the SPOTLIGHT and GLOW trials, CLDN18.2 positivity was defined as $\geq 75\%$ of tumour cells with moderate-to strong membranous staining.

Based on the results of the FAST study, there may be predictive value based on the threshold for CLDN18.2 expression. However, the submission did not present evidence regarding the treatment effect modification of zolbetuximab + chemotherapy for patients who tested positive for CLDN18.2 versus patients who were CLDN18.2- expression using the threshold of $\geq 75\%$. The commentary noted that the variation in treatment effect attributable to CLDN18.2 positivity, isolated from its prognostic effect, could not be established from the evidence presented, and acceptance of the predictive value of the test primarily relies solely on biological plausibility.

¹⁸ Sahin U., et al., (2008), 'Claudin-18 Splice Variant 2 Is a Pan-Cancer Target Suitable for Therapeutic Antibody Development', *Clin Cancer Res*;14 (23): 7624–7634.

Therefore, the value of CLDN18 testing in determining eligibility for zolbetuximab + chemotherapy is unclear, especially given the noninferiority claim regarding efficacy and safety compared to nivolumab + chemotherapy.

13. Economic evaluation

The submission presented a cost-minimisation approach (CMA) comparing zolbetuximab + chemotherapy with CLDN18 testing to nivolumab + chemotherapy with no testing, based on the claim of noninferior efficacy and safety. The commentary considered that CMA is only appropriate if the following are accepted by the PBAC: (i) the place in therapy of zolbetuximab + chemotherapy is first line for metastatic disease and (ii) the clinical claim of non-inferiority in terms of effectiveness and safety. A summary of the cost-minimisation economic evaluation is provided in Table 8.

Table 8 Key components of the CMA provided in the submission

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be noninferior.
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be noninferior.
Evidence base	The main clinical comparison presented in the submission is an indirect comparison of four pivotal trials via network meta-analysis, SPOTLIGHT and GLOW for zolbetuximab and CheckMate 649 and ATTRACTION-4 for Nivolumab.
Equi-effective doses	The equi-effective doses are: zolbetuximab 11,574.72 mg Q3W with CAPOX is equivalent to 5,400.00 mg nivolumab Q3W with CAPOX and zolbetuximab 15,659.91 mg with mFOLFOX6 Q2W is equivalent to 5,280.0 mg nivolumab Q2W with mFOLFOX6.
Direct drug costs	Published price for the twice and thrice weekly regimens of zolbetuximab + CAPOX/mFOLFOX6 or nivolumab + CAPOX/mFOLFOX6.
Other costs or cost offsets	Yes. Infusion costs associated with zolbetuximab with CAPOX/mFOLFOX6 and nivolumab with CAPOX/mFOLFOX6 based on MBS item 13950, Fee: \$123.05. The cost for CLDN18 testing was included and estimated based on the proposed cost of \$112 and a 38.38% positive expression for patients receiving zolbetuximab only.

Source: Table 3-1, p145 and Section 3.2.1, p147 of the submission.

CAPOX = capecitabine and oxaliplatin; CLDN18.2 = Claudin 18.2; CMA = cost-minimisation approach; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin; MBS = Medicare Benefits Schedule; Q2W = once in two weeks; Q3W = once in three weeks.

The submission estimated the cost for CLDN18 testing based on the weighted proportion of patients (38.38%) in SPOTLIGHT and GLOW trials who tested positive for CLDN18.2 expression (defined as $\geq 75\%$ of tumour cells demonstrating moderate-to-strong membranous CLDN18 staining) and a unit cost of \$112 per test. Consequently, the estimated cost to detect one patient with CLDN18.2+ expression was \$291.78. This was considered uncertain pending MSAC advice given that the proposed fee of \$112 per test was based on analogous IHC tests and remains higher than the fees for comparable MBS items (i.e., \$59.60 for generic IHC examination [MBS item 72846]; \$74.50 for IHC testing to determine HER2 [MBS item 72848]; \$74.50 for IHC testing to determine PD-L1 status [MBS item 72814]).

The CMA was conducted to determine the approved ex-manufacturer price (AEMP) of zolbetuximab ensuring that the total cost of treatment with zolbetuximab + chemotherapy, including the cost of CLDN18 testing, is equivalent to the total cost of treatment with nivolumab + chemotherapy. As noted by the commentary, the zero-dollar difference in the total treatment cost was based on the dispensed price for maximum amount (DPMA) rather than the approved ex-manufacturer price (AEMP); however, adjusting the total cost to achieve a \$0 difference using the AEMP resulted in a negligible price increase ($<1\%$). Table 9 presents the results of the cost-minimisation results.

Table 9 Cost minimisation results

Treatment	Split between CAPOX and mFOLFOX6	Testing Cost (\$)	Total Acquisition and Admin Cost (DPMA \$)	Resulting AEMP of zolbetuximab if the cost difference is \$0 based on DPMA	Resulting AEMP of zolbetuximab if the cost difference is \$0 based on AEMP
Zolbetuximab + CAPOX	50%	\$292	\$108,369	\$773.27	\$773.93
Zolbetuximab + mFOLFOX6	50%				
Nivolumab + CAPOX	50%	\$0	\$108,661		
Nivolumab + mFOLFOX6	50%				

Source: Table 3-11, p155 of the submission.

AEMP = approved ex-manufacturer price; DPMA = dispensed price for maximum amount; CAPOX = capecitabine and oxaliplatin; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin

Italics added during evaluation using the 'Attachment 10- VYLOY-CLDN Australia_Cost-min_Section 3-Final.xlsx' to the submission.

As discussed above, the actual proportion of CLDN18.2+ expression in the Australian population remains uncertain. A sensitivity analysis varying the proportion of patients with CLDN18.2+ by $\pm 10\%$ (i.e. 34.5-42.2%) was conducted by the submission. Increasing or reducing the proportion of patients testing positive for CLDN18.2 expression by 10% did not significantly change the price for zolbetuximab. Also, adjusting the proportion of patients with CLDN18.2+ based on prevalence data (i.e., 24-44%) did not impact the derived price for zolbetuximab.

The post-ESC updated results of the CMA based on the published price of nivolumab + chemotherapy and ESC-supported MBS fee of \$74.50 for CLDN18 testing is presented in Table 10.

Table 10 Cost minimisation results – post-ESC updated analysis

Treatment	Split between CAPOX and mFOLFOX6	Testing Cost (\$)	Total Acquisition and Admin Cost based on DPMA (\$)	Resulting AEMP of zolbetuximab if the cost difference is \$0 based on DPMA	Resulting AEMP of zolbetuximab if the cost difference is \$0 based on AEMP
Zolbetuximab + CAPOX	50%	\$194	\$108,466	\$774.03	\$774.70
Zolbetuximab + mFOLFOX6	50%				
Nivolumab + CAPOX	50%	\$0	\$108,661		
Nivolumab + mFOLFOX6	50%				

Source: Table 3-11, p155 of the submission and 'Attachment 10- VYLOY-CLDN Australia_Cost-min_Section 3-Final.xlsx' to the submission.

AEMP = approved ex-manufacturer price; CAPOX = capecitabine and oxaliplatin; DPMA = dispensed price for maximum amount; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin.

Italics indicate post-ESC updates by evaluation group.

14. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the use and costs of CLDN18 testing and zolbetuximab treatment. The commentary considered the estimated cost to the MBS was uncertain due to the following reasons:

- The submission estimated the cost to detect one patient with CLDN18.2+ expression to be \$291.78, based on a weighted proportion of CLDN18.2+ patients in the key clinical trials (38.38%) and proposed MBS item fee for CLDN18 test (\$112). This cost was then applied to patients who were deemed eligible for zolbetuximab. However, the commentary noted that this approach underestimated the actual number of patients likely to undergo the CLDN18 testing if HER2 and CLDN18 are tested together.

Consistent with the testing population, the commentary considered that MBS item fee of \$112 per test should be applied to all eligible patients with advanced GC/GOJ.

- The commentary noted that the financial analysis did not consider the MBS costs associated with intravenous infusions of chemotherapy (MBS item 13950; \$123.05) for both zolbetuximab and nivolumab. Given the duration of treatment is longer with nivolumab compared to zolbetuximab, this would result in a higher number of infusions for nivolumab, potentially leading to a cost-offset for the MBS item related to IV administration.
- In the submission, 80% benefit was assumed for CLDN18 testing to estimate the financial implications to the MBS. The commentary noted that for out of hospital services, the benefit should be 85% of the MBS Schedule fee.

Table 11 summarises the net implications to the MBS as presented in the submission, with revisions made during the commentary.

Table 11 Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of CLDN18 test						
Number of patients tested	Redacted ¹	Redacted ¹	Redacted ¹	Redacted ¹	Redacted ¹	Redacted ¹
<i>Revised number of patients tested^a</i>	<i>Redacted¹</i>	<i>Redacted¹</i>	<i>Redacted¹</i>	<i>Redacted¹</i>	<i>Redacted¹</i>	<i>Redacted¹</i>
Number of patients likely to receive a positive test result	Redacted ²	Redacted ²	Redacted ²	Redacted ²	Redacted ¹	Redacted ¹
Estimated net financial implications of the CLDN18 test to the MBS						
Cost to the MBS less copayments (80% of the proposed MBS schedule fee)	Redacted ³	Redacted ³	Redacted ³	Redacted ³	Redacted ³	Redacted ³
<i>Revised assuming 85% schedule fee^b</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>
<i>Revised using revised number of patients tested, redacted% uptake rate and 85% schedule fee^c</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>
<i>Revised using revised number of patients tested, redacted% uptake rate and 85% schedule fee^c</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>	<i>Redacted³</i>

Source: Table 4-2, p163 and Table 4-16, p175 of the submission; and Attachment 11 – VYLOY CoDep Submission S4 model_Final' workbook to the submission.

CLDN18 = Claudin 18; MBS = Medicare Benefits Schedule.

^a Actual number of patients that would be undergoing CLDN18 test based on PASC advice that CLDN18 testing will be done in all patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma irrespective of HER2 status. (p17, MSAC Application 1767 Ratified PICO Confirmation, April 2024 PASC Meeting).

^b Revised by assuming 85% MBS benefit as for out of hospital services.

^c Revised by using updated number of patients with advanced or metastatic G/GOJ adenocarcinoma with ECOG PS of 0-1 as estimated by the submission and assuming redacted% uptake rate for the CLDN18 test and 85% MBS benefit.

^d Revised by using updated number of patients with advanced or metastatic G/GOJ adenocarcinoma with ECOG PS of 0-1 as estimated by the submission and assuming redacted% uptake rate for the CLDN18 test and 85% MBS benefit.

Italics revised during evaluation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² <500

³ \$0 to < \$10 million

According to the proposed updated MBS item descriptor, which includes a practice note specifying that CLDN18 testing should be pathologist determinable, CLDN18 testing may be performed following a negative HER2 test. The financial impact to the MBS estimated by the commentary may be overestimated if CLDN18 tests are performed following a negative HER2

test, resulting in a cost of **\$0 to < \$10 million** to the MBS over six years of listing, compared to **\$0 to < \$10 million** if all eligible patients with advanced G/GOJ are tested for both HER2 and CLDN18.

Table 12 presents the estimated use and financial implications in the submission and revised financial implications using the post-ESC calculated cost-minimised AEMP of \$774.03 for zolbetuximab and ESC-supported MBS fee of \$74.50 for CLDN18 testing.

Table 12 Estimated use and financial implications- post-ESC updated analysis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of CLDN18 test						
Number of patients tested	Redacted ¹	Redacted ¹	Redacted ¹	Redacted ¹	Redacted ¹	Redacted ¹
Number of patients likely to receive a positive test result (38.38% positivity rate)	Redacted ²	Redacted ²	Redacted ²	Redacted ²	Redacted ¹	Redacted ¹
Estimated extent of use of zolbetuximab						
Number of patients likely to be treated with proposed drug	Redacted ²	Redacted ²	Redacted ²	Redacted ²	Redacted ²	Redacted ¹
Number of scripts dispensed	Redacted ³	Redacted ³	Redacted ³	Redacted ³	Redacted ³	Redacted ³
Number of scripts dispensed offset	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Estimated financial implications of zolbetuximab to the PBS/RPBS						
Cost to PBS/RPBS less copayments	Redacted ⁴	Redacted ⁴	Redacted ⁴	Redacted ⁵	Redacted ⁵	Redacted ⁵
<i>Revised by using the AEMP of \$774.03 for zolbetuximab</i>	Redacted ⁴	Redacted ⁴	Redacted ⁴	Redacted ⁵	Redacted ⁵	Redacted ⁵
Estimated financial implications for nivolumab to the PBS/RPBS						
Cost to PBS/RPBS less copayments	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶
Estimated financial implications to the MBS (assuming 80% benefit)						
Cost to the MBS less copayments for CLDN18 test	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
<i>Revised by using an ESC-supported MBS fee of \$74.50 for CLDN18 testing</i>	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Cost to the MBS less copayments for IV administration	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
<i>Revised to include the MBS cost associated with IV infusion for both zolbetuximab and nivolumab.</i>	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶
Net financial implications						
Net cost to PBS/RPBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
<i>Revised net cost to PBS/RPBS</i>	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
<i>Revised net cost to MBS</i>	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to PBS/RPBS/MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
<i>Revised net cost to PBS/RPBS/MBS</i>	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Sensitivity Analyses						
Assuming 43.38% of patients are CLDN18.2+ (base case: 38.38%)^a						
Net cost to PBS/RPBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to MBS	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶	Redacted ⁶
Net cost to PBS/RPBS/MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Assuming 33.38% of patients are CLDN18.2+ (base case 38.38%)						

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost to PBS/RPBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to PBS/RPBS/MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Assuming 5% of patients tested undergo re-biopsy and re-testing (base case: no re-testing or re-biopsy)						
Net cost to PBS/RPBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Cost of re-testing and re-biopsy	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷
Net cost to PBS/RPBS/MBS	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷	Redacted ⁷

Source: Attachment 11 – VYLOY CoDep Submission S4 model_Final' workbook to the submission.

AEMP = Approved Ex-Manufacturer Price; CLDN18.2 = Claudin 18.2; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a The cost-minimised AEMP of zolbetuximab changed from \$774.03 to \$774.20 when using the upper bound of prevalence rate (43.38%)

^b The cost-minimised AEMP of zolbetuximab changed from \$774.03 to \$773.81 when using the lower bound of prevalence rate (33.38%)

^c The cost of re-biopsy was based on MBS item 30694 (100% fee: \$641.80)

Italics indicate post-ESC analysis by evaluation group.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² <500

³ 5,000 to < 10,000

⁴ \$40 million to < \$50 million

⁵ \$50 million to < \$60 million

⁶ net cost saving

⁷ \$0 to < \$10 million

15. Other relevant information

Nil.

16. Committee-In-Confidence information

REDACTED

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- CLDN18.2 expression may have prognostic impact on gastric cancer. This affects the comparison between the nivolumab trial (unknown CLDN18.2 status) and the zolbetuximab trial (in CLDN18.2 – positive patients). A recent systematic review and meta-analysis by Moraes et al. (2024) concluded that, CLDN18.2 expression is a negative prognostic indicator for overall survival in gastric cancer patients. Other studies on the prognostic impact of CLDN18.2 expression were based on small, retrospective, single-institution studies without a validation cohort. In addition, the evidence supporting the efficacy and safety of zolbetuximab was limited to patients with CLDN18.2-positive (CLDN18.2+) tumours, whereas CLDN18.2 expression status was not assessed in the nivolumab trials.
- SPOTLIGHT and GLOW key trials only included patients who were positive for CLDN18.2 at a threshold of ≥75% of tumour cells with moderate-to-strong membranous CLDN18 immunohistochemistry (IHC) staining.

Economic issues

- A cost-minimisation approach is appropriate if PBAC accepts that zolbetuximab in combination with chemotherapy as a first line treatment for patients with G/GOJ adenocarcinoma who test positive for CLDN18.2 expression has noninferior efficacy and safety.

Financial issues

- The estimated cost to the Medicare Benefits Schedule (MBS) was uncertain due to uncertainty regarding the prevalence of patients with G/GOJ adenocarcinoma who test positive for CLDN18.2 expression in Australia, potential underestimation of testing uptake, and exclusion of chemotherapy infusion and adverse event costs. The updated analysis demonstrates potential impact to be likely low; however, uncertainty regarding additional costs remain.

Other issues

- There was insufficient justification of the proposed fee of \$112. Given that comparable MBS listed IHC tests for PD-L1 and HER2, which use similar methodology to the proposed CLDN18 test, have a fee of \$74.50 and the submission provided insufficient rationale for the CLDN18 test to have a higher fee than PD-L1 and HER2 IHC tests. The ESCs advised that aligning the fee to \$74.50 would be appropriate.
- The proposed test and clinical utility standard, Ventana® CLDN18 (43-14A) RxDx assay is not listed on the Australian Register of Therapeutic Goods (ARTG), and no registration details or update were provided in the submission. Additionally, in its pre-ESC response, applicant stated that the Therapeutic Goods Administration (TGA) has approved the assay but is awaiting registration of zolbetuximab prior to the assay being listed on the ARTG. The applicant is requested to provide an update on registration in its pre-MSAC response.
- Appropriate pathologist training and quality assurance programs for diagnostic tests targeting the CLDN18.2 will be required.

ESCs discussion

The ESCs noted that the integrated codependent application sought Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for the evaluation of Claudin 18.2 (CLDN18.2) expression to determine patient eligibility for zolbetuximab (VYLOY®) in combination with chemotherapy on the Pharmaceutical Benefits Scheme (PBS) for patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma.

The ESCs noted and welcomed public consultation feedback from two professional organisations and one consumer organisation. ESC noted the feedback from Royal College of Pathologists of Australasia (RCPA) that supported the proposed fee. The feedback highlighted that stringent assay validations along with pathologist training and ongoing quality control requirements contribute to higher test costs.

The ESCs noted that the proposed test and clinical utility standard, Ventana® CLDN18 (43-14A) RxDx assay, is not yet listed on the Australian Register of Therapeutic Goods (ARTG), and no registration details or update were provided in the submission. The ESCs further noted the applicant's pre-ESC response confirmed that the Therapeutic Goods Administration (TGA) has approved the assay but is awaiting zolbetuximab registration before listing it on the ARTG.

The ESCs noted the population, intervention, comparator and outcomes (PICO) that had been ratified by the PICO Advisory Subcommittee. The ESCs acknowledged the applicant's pre-ESC

response, which confirmed that the proposed target population for both testing and treatment includes patients with locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma and excludes patients with oesophageal adenocarcinoma. The ESCs noted that this population is consistent with the pivotal trials. The ESCs further noted that patients who are found to be HER2-negative and CLDN18.2-positive advanced G/GOJ adenocarcinoma will have an additional treatment option with zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy as a novel first-line therapy.

The ESCs noted the proposed MBS item descriptor and the proposed fee. The ESCs agreed that the proposed MBS item should be pathologist-determinable, and that the item descriptor should specify 'specialists and consultant physicians' as requestors. The ESCs considered it is appropriate to test CLDN18.2 in parallel with HER2 using IHC/ *in situ* hybridization (ISH) testing methods as it minimises the need for additional biopsy samples.

The ESCs noted the comparable existing MBS listings for IHC tests such as program death-ligand 1 (PD-L1) and acknowledged that the proposed test would use a similar methodology in processing, staining and scoring of the specimen. Given that the existing MBS listed IHC tests of PD-L1 have a fee of \$74.50 and that the CLDN18.2 test uses similar methodology, the ESCs considered the proposed fee of \$112.00 to be high. Consequently, the ESCs considered a fee with \$74.50 would be more appropriate. Further to this, the ESCs noted that existing generic MBS items, such as 72846, 72847, 72849 and 72850, could be used to claim CLDN18.2 IHC testing in addition to HER2 IHC as add-on tests. However, the ESCs noted the current application was requesting a separate MBS item for CLDN18 IHC testing.

The ESCs noted the clinical evidence suggested adding zolbetuximab to standard chemotherapy for CLDN18.2-positive patients improves survival by 2.2–2.7 months compared to chemotherapy alone.

The ESCs considered that the Ventana® CLDN18 (43-14A) RxDx IHC assay demonstrated good to excellent analytical performance with high sensitivity (94%) and specificity (97%). The ESCs considered the analytical performance of Ventana® CLDN18 testing demonstrating high reproducibility across reagent lots, instruments, between days, laboratory sites, and pathologist interpretations. In addition, the ESCs noted clinical performance of the assay showed 96% accuracy and a high positive predictive value of 96%. However, the ESCs noted that the semi-quantitative nature of IHC testing and the potential for subjective interpretation, meant that performance metrics are reliant on consistent IHC interpretation across pathologists. Therefore, the ESCs emphasised the importance of appropriate pathologist training in semi-quantitative IHC interpretation and the establishment of an external quality assurance program (EQAP). The ESCs noted that different antibodies (e.g., Ventana, LSBio, Novus) and platforms (e.g., Dako, Ventana) are commercially available and can be used to perform IHC staining for evaluation of CLDN18.2 status in gastric cancer tissues. The ESCs further noted that performance differences across platforms exist. Therefore, the ESCs highlighted the importance of validating protocols for specific antibody-platform combinations. The ESCs noted that IHC testing is well established in Australia and considered, regardless of the assay or platform used in Australian laboratories, a high degree of correlation with the clinical utility standard could be expected.

The ESCs noted no data was provided to establish stability of CLDN18.2 in formalin-fixed paraffin-embedded (FFPE) tissue blocks or tissue microarray (TMA) sections, except for 3-month stability as demonstrated in the Global Ring study (Jasani et al 2024). However, the ESCs considered it reasonable to expect limited loss of CLDN18 antigenicity when being preserved for up to a year.

The ESCs noted the study by Kim et al., 2024¹⁹ reported that intratumor heterogeneity in CLDN18.2 expression exists, which could be addressed by testing multiple biopsies from the same tumour to improve sensitivity. Furthermore, the ESCs noted that it is standard practice in Australian laboratories performing IHC testing to test 2-8 biopsies, particularly as endoscopic biopsies may not fully represent the entire tumour.

The ESCs noted that zolbetuximab is a monoclonal antibody that targets and binds to the CLDN18.2 protein. However, the proposed Ventana® CLDN18 (43-14A) RxDx assay does not target specific isoforms of CLDN18. Therefore, both CLDN18.1 (mainly expressed in lung tissue) and CLDN18.2 (mainly expressed in gastric tissue) are detected by this test. The submission stated that testing of gastric tissue with the Ventana® CLDN18 (43-14A) RxDx assay would produce a result that is reflective of the CLDN18.2 level. However, the ESCs noted that is unclear to what extent CLDN18.1 is expressed in gastric tissue and therefore the CLDN18.2 level has the potential to be overestimated. The ESCs noted one study (Sahin et al., 2008) that suggested CLDN18.2 is a lineage-specific marker that is highly selective for short-lived gastric epithelial cells and is absent from healthy tissues, meanwhile CLDN18.1 is predominantly expressed in lung tissue. Therefore, the ESCs considered that the CLDN18.2 is a highly selective gastric lineage marker expressed in short-lived differentiated cells but not in the stem cell zone of the stomach mucosa. The ESCs concluded that it is likely that the results following testing of gastric tissue using the Ventana® CLDN18 (43-14A) RxDx assay would be reflective of the CLDN18.2 expression level and would therefore appropriately select patients for zolbetuximab treatment.

The ESCs noted the submission presented retrospective studies across which CLDN18.2 expression levels were not reliably prognostic of overall survival (OS) outcomes. However, the commentary presented a recent systematic review and meta-analysis by Moraes et al. (2024,) which concluded that CLDN18.2 expression is a negative prognostic indicator for OS in these patients. The ESCs noted that the Moraes analysis showed a non-significant effect on progression-free survival (PFS) and included in the meta-analysis had varying definitions of a modest effect on OS (Hazard ratio (HR) for prolonged OS for CLDN18.2 negative status: 1.20; 95% CI: 1.07-1.34; p<0.01). The study looked specifically at CLDN18.2 negative status, rather than the predictive effect of a high CLDN18.2 positivity. Overall, the ESCs concluded that the available evidence suggests that expressing CLDN18.2 is possibly prognostic of poorer health outcomes in gastric cancer, but the quality and applicability of this evidence to the proposed Australian clinical population is uncertain.

The ESCs noted that the Ring study (Jasani et al 2024), which used Ventana® CLDN18 (43-14A) RxDx assay, defined a positive result for CLDN18.2 as ≥75% of tumour cells showing moderate-to-strong membranous staining above the background level. The ESCs also noted that the SPOTLIGHT and GLOW trials included only patients who were positive for CLDN18.2 at a threshold of ≥75% of tumour cells with moderate to strong membranous CLDN18.2 IHC staining.

The ESCs noted the claim of non-inferior safety for the test compared to no testing. As CLDN18.2 testing is conducted alongside HER2 IHC/ISH as part of the standard diagnostic process, it does not introduce extra safety burdens. The ESCs considered that the test posed no additional safety concerns and that adverse events related to testing were minimal. Overall, the ESCs concluded that the claim of non-inferior safety compared to no testing was appropriate.

The ESCs noted the economic model was based on a cost minimisation analysis (CMA) approach comparing zolbetuximab in combination with chemotherapy with CLDN18 testing, to nivolumab in combination with chemotherapy with no testing based on the noninferiority claim of efficacy and

¹⁹ Kim T.-Y et al (2024), Clinicopathological analysis of claudin 18.2 focusing on intratumoral heterogeneity and survival in patients with metastatic or unresectable gastric cancer. *ESMO Open*;9 (12)

safety. The ESCs agreed with the commentary that a CMA would be appropriate if the claims of noninferior efficacy and safety are accepted and that zolbetuximab plus chemotherapy is indicated as a first line of treatment for patients with metastatic disease. The ESCs further noted the applicant's updated analysis which suggested the test costs would have minimal impact. However, the ESCs advised that there were a number of issues to be resolved that will have an impact on the results of the CMA.

The ESCs noted the financial implications were based on an incidence-based epidemiological approach. However, the ESCs noted several limitations, including uncertainty around the prevalence of patients with G/GOJ adenocarcinoma, potential underestimation of the number of patients undergoing CLDN 18 testing and re-testing, exclusion of costs associated with intravenous infusions of chemotherapy and assumed lower rebate. While the ESCs acknowledged the updated financial analysis provided in the pre-ESC response, which addressed some of the concerns, they advised that a revision of the financial analysis would be required to address the aforementioned uncertainties and also to take into account the ESC supported test fee of \$74.50 (Table MSAC.11 presents updated post-ESC analysis). The ESCs further noted that the financials will still be an underestimate given the model could have been structured to better account for cost of adverse events.

18. Applicant comments on MSAC's Public Summary Document

The applicant acknowledges MSAC's support for the co-dependent listing of zolbetuximab and CLDN18 IHC testing. We agree with MSAC's interpretation of the clinical and economic evidence, including the biological rationale for co-dependence. We also note the importance of implementation support, including quality assurance and pathologist training, to ensure accurate and consistent testing across pathology centres.

19. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)