MSAC Application 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

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for Immunohistochemistry (IHC) testing for CLDN18.2 expression in gastric or gastroesophageal junction adenocarcinoma

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 HER2-negative G/GOJ adenocarcinoma who are found positive after claudin testing (CLDN18.2+).
Prior tests	None
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/s	Test: No testing Drug: For patients without prior immune checkpoint inhibitor 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/metastatic disease, chemotherapy alone appeared to be the appropriate comparator (to be confirmed by PBAC).
Clinical utility standard (for codependent tests only)	Ventana® CLDN18 (43-14A) RxDx Assay; a positive result corresponds to ≥75% tumour cells (TCs) showing moderate-to-strong membranous staining above background, while <75% TCs showing moderate-to-strong membranous staining was indicative of a negative result. Patients who have locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma which are CLDN18.2+ will be eligible for zolbetuximab treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.
Outcomes	Test outcomes: 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,

Component	Description
	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. <u>Drug-related outcomes</u>: Safety outcomes: 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: • 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: • 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.
Assessment questions	What is the safety, effectiveness, cost-effectiveness and total costs of CLDN18.2 testing and treatment with zolbetuximab versus no testing and treatment with nivolumab in patients with locally advanced unresectable or metastatic HER2 negative G/GOJ adenocarcinoma? Does testing for CLDN18.2 predict a treatment effect modification with zolbetuximab? What are the potential costs and cost offsets associated with disease management arising from the listing of CLDN18.2 testing?

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing[1] of immunohistochemical (IHC) testing for Claudin18.2 expression to determine eligibility for relevant treatment for patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of zolbetuximab, a monoclonal antibody targeting CLDN18.2, for patients with CLDN18.2+, HER2-negative, locally advanced unresectable or metastatic G/GOJ adenocarcinoma.

The use of the proposed technology results in noninferior health outcomes compared to no testing. At the pre-PASC teleconference, the applicant stated that the noninferiority clinical claim pertained to the entire pathway, and not only the test component.

PICO criteria

Population

Test population

The population eligible for CLDN18.2 testing includes all patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma who are treatment naïve for this disease stage. The key trials (GLOW and SPOTLIGHT) did not describe the population that had undergone CLND18.2 testing. Therefore, the proposed testing population relative to the two trials could not be appraised.

PASC queried whether the proposed testing is intended prior to first line treatment in the advanced setting or whether the testing should be extended for use prior to second line treatment as well. The applicant's clinical expert noted that zolbetuximab was trialled in the key studies (GLOW and SPOTLIGHT) as a first line treatment in the advanced setting, and hence the proposed testing is intended prior to first line treatment in the advanced setting. PASC agreed with the applicant that the proposed population should align with that of the key trials.

PASC acknowledged the applicant's revised approach for CLDN18.2 testing to be performed in parallel with HER2 testing, and therefore the testing population will include all patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma, regardless of HER2 status which would be unknown at the time of CLDN18.2 testing. The applicant's clinical expert suggested this population would be made up of approximately 60% of patients who have de novo locally advanced unresectable/metastatic disease, and 40% who have previously diagnosed disease that has progressed from an earlier stage (for which most/all would have received treatment) into locally advanced unresectable/metastatic disease. The applicant stated that parallel testing was a better approach than sequential testing as it minimised workflow and allowed for timely treatment decisions. Furthermore, PASC noted from the applicant's pre-PASC response

[1] The application initially requested MBS listing of Claudin 18.2 testing to determine access to zolbetuximab in patients with HER2-negative, locally advanced unresectable or metastatic G/GOJ adenocarcinoma. Through the PASC process, the population was changed to include all patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma irrespective of HER2 status to allow for parallel testing of HER2/CLDN 18.2 and the treatment eligibility was not restricted to zolbetuximab. This was confirmed by PASC.

that parallel testing allows for the efficient use of limited biopsy material, thereby reducing the need for repeated invasive procedures, and that parallel testing aligns with the European-Australasian consensus on the management of advanced gastric and gastro-oesophageal junction cancer treatment guidelines (Pavlakis et al 2022).

PASC considered whether parallel testing would result in redundancy if clinicians have decided to treat patients with treatment options other than zolbetuximab (for example nivolumab) regardless of test outcomes. However, the applicant's clinical expert emphasized that parallel testing provides more comprehensive information about the patient's tumour profile upfront, facilitating more informed decision-making regarding the optimal first line treatment in the advanced setting based on all the treatment options suitable for the patient. PASC accepted the applicant's advice that parallel testing may facilitate better timing of management decisions and is best practice for treatment considerations. PASC also noted the applicant's pre-PASC response suggested to define one single population diagnosed with locally advanced unresectable/metastatic disease, of which a subset of patients will have received nivolumab treatment as adjuvant therapy for Stage II or III disease which has subsequently relapsed into unresectable/metastatic disease. PASC confirmed that the population will consist of one single population with locally advanced unresectable/metastatic disease who are treatment naïve for this disease stage.

Drug population

Patients eligible for zolbetuximab must be diagnosed with locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma and found to be CLDN18.2+. This population is consistent with the treatment population in key trials (GLOW and SPOTLIGHT).

Background and rationale for testing CLDN18.2

G/GOJ cancer arises from the epithelial lining of the stomach and the GOJ (the area located between the stomach and the oesophagus), respectively. Globally, gastric cancer (GC) is the fifth most common type of cancer and third leading cause of cancer related deaths with more than one million new cases and an estimated 769,000 deaths in 2020. GOJ adenocarcinomas are the ninth most common cancer, with over 600,000 new cases annually and resulting in 544,000 deaths worldwide (Sung et al. 2021). Adenocarcinoma is the most common G/GOJ cancer histological type, representing 85% of all G/GOJ cancer cases diagnosed.

Early-stage G/GOJ cancer is often asymptomatic, while later stages often present with non-specific symptoms such as dysphagia, asthenia, indigestion, vomiting, stomach pain, bloating, weight loss, early satiety and/or iron deficiency anaemia (Pellino et al. 2021). The lack of specific or pathognomonic symptoms prevents early diagnosis in the absence of screening programs and it is estimated that 80–90% of patients in Western countries will present with locally advanced or metastatic tumours that are minimally resectable (Bickenbach and Strong 2012). Although multimodal treatments, including curative surgery and perioperative/adjuvant chemotherapy have improved outcomes in patients with early-stage disease, the prognosis in those with advanced cancer remains poor (Van Cutsem et al. 2016).

In Australia, GC is less common relative to global estimates, representing the 15th most diagnosed cancer in 2020. In Australia, approximately 2000 new cases of GC are diagnosed each year, and the incidence of GOJ cancers is rising (Abbas et al. 2021). Australian data shows that patients with G/GOJ cancer had a 30% chance of surviving 5 years compared with the general population (AIHW 2018). Males were 2.1 times as

likely to be diagnosed with G/GOJ cancer and 2.0 times more likely to die from G/GOJ cancer compared to females (AIHW 2018). Indigenous Australians were 1.5 times as likely to be diagnosed with G/GOJ cancer and 1.6 times as likely to die from G/GOJ cancer compared to non-Indigenous Australians. Australians in the lowest socioeconomic group were 1.3 times as likely to be diagnosed with G/GOJ cancer and 1.4 times as likely to die from the same compared with Australians in the highest socioeconomic group (AIHW 2018).

Patients with locally advanced unresectable/metastatic cancer are further classified according to human epidermal growth factor receptor 2 (HER2) status. HER2 testing is done as part of the standard work up for G/GOJ cancer diagnosis and staging. A tumour is defined as being HER2-negative if a lack of HER2 expression is confirmed by an IHC score of 0, 1+, or by an IHC score of 2+ combined with a confirmation of the tumour's HER2 negative status by in-situ hybridization (ISH) testing. An Australian study (Kumarasinghe et al. 2017) estimated 86.1% of patients with G/GOJ cancer were HER2-negative. The current first-line treatment options in the Australian context for patients with locally advanced unresectable/metastatic HER2-negative G/GOJ cancer are platinum plus fluoropyrimidine-containing chemotherapy (PF chemo) with or without nivolumab. The application proposed a new treatment option with Zolbetuximab (immunoglobulin G1 monoclonal antibody) for patients with locally advanced unresectable/metastatic HER2-negative G/GOJ cancer that are also found to be CLND18.2+.

Claudins are a protein which represent essential components of tight cell junctions in epithelial cells. One of the most important is claudin-18 (CLDN18), which is located on the cell membrane/surface. It plays a pivotal role in maintaining barrier function and cell polarity promoting acid resistance (Chen et al. 2023; LaFemina et al. 2014). During malignant transformation, the loss of cell polarity exposes the epitope of CLDN18, making it more accessible to antibodies (Cao et al. 2022). Zolbetuximab, mediates antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity in CLDN18.2+ G/GOJ adenocarcinoma cells. Therefore, the population under consideration is required to undergo CLDN18.2 testing to determine eligibility for zolbetuximab.

Estimated utilisation

Based on the annual incidence of GC estimated in 2021, and applying an annual population growth rate of 2.2%, the application estimated the incidence of GC in 2025 to be 2,808. Further, it was estimated that 84.08% of all gastric cancers are of adenocarcinoma histology out of which 84% were categorised as Stages II-IV and most corresponded to advanced or metastatic disease (90%). The number of tumours that were categorised as HER2 negative were based on an Australian study (Kumarasinghe et al. 2017) that estimated 86.1% of patients with G/GOJ cancer were HER2-negative. The application assumed an uptake of the test of 90% of the eligible patients and based on the key trials, SPOTLIGHT and GLOW, the proportion of patients with G/GOJ cancer with CLDN18.2+ expression (≥ 75%) was 38%. Of those patients with tumours found to be CLDN18.2+, the application assumed 95% would receive zolbetuximab. A summary of the estimated uptake of CLDN18.2 testing and zolbetuximab is presented in Table 2. The utilisation estimates presented in Table 2 are based on CLDN18.2 testing being performed after HER2 testing (i.e. sequential testing as initially proposed by the applicant). As CLDN18.2 testing is proposed to be performed in parallel with HER2 testing in the current proposal, the number of patients undergoing CLDN18.2 testing will be more than initially estimated. By assuming that all patients will be tested for CLDN18.2 expression regardless of the HER2 status, the number of patients who are tested for CLDN18.2 will increase, to equal the number of patients diagnosed with advanced or metastatic disease (e.g. 1787 patients in 2025, according to Table 2 below). The number of patients estimated to be treated with zolbetuximab (as per

Table 2) would not increase with parallel testing if the PBS use is restricted to patients who are HER2 negative and CLDN18.2 positive.

The proposed uptake rate (95%) of zolbetuximab in patients with CLDN18.2+ expression is likely overestimated. Clinicians are familiar with immune checkpoint inhibitor therapies such as nivolumab, and uptake rates of novel drugs are typically graduated. The application proposed that zolbetuximab is noninferior to nivolumab and has not provided justification for why it anticipates clinicians will prefer zolbetuximab over nivolumab in 95% of patients with CLDN18.2+ expression from year 1 onwards.

Table 2: Estimated uptake of Claudin18.2 testing and treatment with zolbetuximab

Parameter	Value used	Year					
		2025	**2026**	**2027**	**2028**	**2029**	**2030**
Gastric cancer patients (incidence)		2808	2870	2934	2999	3065	3133
Number with adenocarcinoma histology (G/GOJ cancer)	84.08%	2361	2414	2467	2522	2578	2635
Stage II/III	56.80%	1342	1372	1402	1433	1465	1497
Stage IV	27.20%	*643*	*657*	*672*	*868*	*702*	*717*
Stage II-IV	*84%*	*1985*	*2029*	*2074*	*2119*	*2167*	*2214*
Number diagnosed with advanced or metastatic disease	90.00%	*1787*	*1827*	*1867*	*1908*	*1951*	*1993*
Number of patients with G/GOJ adenocarcinomas who are HER2 negative[b]	86.10%	*1539*	*1574*	*1608*	*1643*	*1680*	*1716*
Number of patients tested for CLDN18.2[a]	90.00%	*1386*	*1417*	*1448*	*1479*	*1512*	*1545*
Number of patients CLDN18.2 expression (≥ 75%)[b]	38.40%	*533*	*545*	*557*	*568*	*581*	*594*
Number of patients CLDN18.2 expression (≥ 75%)[b] using zolbetuximab[c]	95.00%	*507*	*518*	*530*	*540*	*552*	*565*

Source: HPP200118 - VYLOY_Ventana_AU_Utilisation_v0.2 excel workbook provided with the application
G/GOJ = Gastric or gastro-oesophageal junction cancer, CLDN18.2 = Claudin 18 splice variant 2
a The estimates presented are based on CLDN18.2 testing being performed after HER2 testing (i.e. sequential testing as initially proposed by the applicant). As CLDN18.2 testing is proposed to be performed in parallel with HER2 testing in the current proposal, the number of patients undergoing CLDN18.2 testing will be more than initially estimated.
b The CLDN18.2 threshold for a positive result is ≥75% tumour cells showing moderate-to-strong membranous staining using Ventana® CLDN18 (43-14A) RxDx Assay
c Both PASC and the applicant's clinical expert agreed this was an unrealistically high uptake rate in the context of a new, non-inferior treatment option. It may be reasonable to anticipate a graduated increase in the uptake rate for each subsequent year zolbetuximab is listed.
Italics: The application made a cell referencing error while calculating the Stage IV patient numbers. This was corrected during the PICO development and numbers in italics represents the corrected values.

Prior tests

PASC noted that with the applicant's revised parallel approach, there are unlikely to be any relevant prior tests in the population, noting some patients may have had testing performed at an earlier stage of their disease.

Intervention

The application has proposed MBS listing of Ventana® CLDN18 (43-14A) RxDx Assay, a semi-quantitative IHC assay using mouse monoclonal anti-claudin 18 antibody, intended for laboratory use in the assessment of CLDN18.2 protein in formalin-fixed, paraffin-embedded (FFPE) G/GOJ cancer tissue specimens by light microscopy. The Ventana® CLDN18.2 (43-14A) RxDx Assay threshold for a positive result is ≥75% tumour cells (TCs) showing moderate-to-strong membranous staining above background, while <75% TCs showing moderate-to-strong membranous staining is indicative of a negative result. A positive result (CLDN18.2+) will aid in determining the patient's eligibility for zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy.

In normal gastric epithelial tissue, claudins in tight junctions are inaccessible from either the apical or basal surface, as they perform their role in tightly binding adjacent epithelial cells. Malignant transformation in gastric cancer disrupts the tight junctions and normal cell polarity, resulting in aberrant cell surface exposure of CLDN18.2 epitopes, exposed on the tumour cell surface in G/GOJ tumour tissue. These CLDN18.2 epitopes may be targeted by monoclonal antibody therapies, such as zolbetuximab. The prognostic effect of CLDN18.2 expression may be informative while evaluating the clinical efficacy of zolbetuximab. There is some published evidence addressing the prognostic effect of CLDN18.2 expression in patients diagnosed with G/GOJ cancer. According to one study (Lu et al. 2020), low expression of Claudin-18 indicated poor clinical prognosis of GC. Another study (Kayikcioglu et al. 2023) which investigated the prognostic value of CLDN18.2 expression suggested CLDN18.2 is not a prognostic marker in patients with gastric adenocarcinoma, although it is predictive. Evidence on the prognostic value of CLDN18.2 expression in patients with G/GOJ cancer may be informative and should be presented by the applicant when submitting the co-dependent technology application to MSAC and PBAC.

In the management of metastatic G/GOJC, taking biopsy specimens is currently part of standard practice and diagnostic work-up (MBS Item 30694). The application proposed that CLDN18.2 expression testing can be carried out on the tissue sample used to establish the initial diagnosis (G/GOJC).

During the pre-PASC teleconference, the applicant stated there is no evidence as to how long archival tissue can be held and remain viable for analysis of CLDN18.2 status (before fresh tissue is required), but that studies on this topic are underway and information is forthcoming. According to the application, samples in the phase III trials (GLOW and SPOTLIGHT) were primarily archival; however, in some cases fresh tissue was used. It is unclear whether fresh tissue samples would be required for patients with previously diagnosed early-stage disease who have previously undergone biopsy, diagnostic workup and treatment (which may include HER2 testing) and who have subsequently experienced disease recurrence which has progressed to the advanced/metastatic setting. Disease recurrence may be diagnosed through needle aspiration cytology (e.g., lymph node or liver/lung/bone metastases), which is not traditionally amenable to IHC testing. There is no known role for CLDN18.2 testing in monitoring a patient's response to zolbetuximab treatment.

IHC testing is a well-established technique in all major pathology laboratories and is currently performed on this target population to determine HER2 status (MBS Item 72848). Therefore, these laboratories already have the platform infrastructure to perform CLDN18.2 IHC testing. The relevant reagents (including

the CLDN18.2 antibody) will be available upon listing of the VENTANA CLDN18 (43-14A) RxDx Assay on the ARTG. A certified pathologist would be responsible for conducting the testing and reporting of results. It is proposed that CLDN18.2 IHC testing be carried out in a pathology laboratory meeting the appropriate accreditation standards.

The application stated that pathologist training and quality assurance programs would be developed with respect to delivery of diagnostic tests for access to treatments targeting the CLDN18.2 pathway on the PBS. This would address interpretation of the test results for CLDN18.2 positivity specific to the Ventana® CLDN18 (43-14A) RxDx Assay. In addition, the applicant is planning to facilitate one-day peer-to-peer workshops for Australian pathologists, with training effectiveness assessed for those who participate. The applicant claimed that this process would result in pathologists having greater experience in performing the test and applying the scoring methods in a manner that will help to ensure consistency between laboratories.

In the absence of the proposed test and therapy, all patients with locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma would be eligible to receive nivolumab in combination with chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug, if not otherwise contraindicated (PBS code 13121NMP).

PASC noted the application assumed zolbetuximab would have an uptake rate of 95% of eligible patients with tumours found to be CLDN18.2+. Both PASC and the applicant's clinical expert agreed this was an unrealistically high uptake rate in the context of a new, non-inferior treatment option. PASC considered that it may take time to change the prescribing behaviour of oncologists. Therefore, it is expected only a minority of patients who are CLDN18.2+ will receive zolbetuximab initially, and many CLDN18.2+ patients will receive nivolumab. However, it may be reasonable to anticipate a graduated increase in the uptake rate for each subsequent year zolbetuximab is listed.

Comparator(s)

The comparator proposed by the application is "no testing", as testing for CLDN18.2 is not currently funded, nor available in Australia (currently under TGA review). Patients with tumours that are HER2-negative but are not tested for CLDN18.2 will be eligible for nivolumab in combination with chemotherapy, for example, FOLFOX (oxaliplatin + folinic acid + fluorouracil). There is no recommendation for one specific chemotherapy. The choice of regimen depends on patient characteristics, previous treatment and clinician choice. Nivolumab was the first immunotherapy to be listed on the PBS for the treatment of the target population: recommended by the PBAC in March 2022 and PBS listed 1 October 2022. It is noted that pembrolizumab, an immune checkpoint inhibitor (ICI), was recommended by the PBAC at the May 2022 intra-cycle meeting (pembrolizumab PSD, November 2021 PBAC Meeting with March 2022 and May 2022 Addendums), however is not currently listed for this indication on the PBS website.

The subgroup of the population who have relapsed following early-stage disease treatment with nivolumab, would be ineligible for nivolumab in the locally advanced unresectable/metastatic disease setting. In these patients, the test comparator is no testing while the most appropriate drug comparator (to be confirmed by PBAC) appeared to be chemotherapy alone. For this subgroup of patients, zolbetuximab + chemotherapy may represent a superior treatment option compared to chemotherapy alone, based on the efficacy data of the key trials (GLOW and SPOTLIGHT).

PASC and the applicant's clinical expert agreed that in addition to biomarker status and clinician/patient preference, a number of factors may determine whether a patient may receive nivolumab, zolbetuximab or chemotherapy alone.

PASC and the applicant's clinical expert agreed that eligible patients who have relapsed following early-stage disease treatment with nivolumab would likely be treated with zolbetuximab + chemotherapy, as the PBS restriction precludes repeated PD-1/PD-L1 inhibitor therapy for this disease. In addition, eligible patients who have contraindications for nivolumab, such as pre-existing autoimmune disease, may be treated with zolbetuximab + chemotherapy. It would be reasonable to assume a high uptake rate of zolbetuximab in these patient subgroups, given the apparent superior efficacy of zolbetuximab + chemotherapy compared to placebo + chemotherapy demonstrated in the key trials SPOTLIGHT and GLOW, however these remain individualised decisions. PASC noted careful consideration of the treatment comparator for these subgroups of the target population would be required, but that confirming the appropriate comparator for the medicine is a matter for PBAC.

Clinical utility standard (for codependent investigative technologies only)

The key trials presented by the submission (SPOTLIGHT and GLOW) utilised the Ventana® CLDN18 (43-14A) RxDx Assay. The CLDN18.2 threshold for a positive result was ≥75% TCs showing moderate-to-strong membranous staining above background, while <75% TCs showing moderate-to-strong membranous staining was indicative of a negative result. The application stated that the VENTANA CLDN18 (43-14A) RxDx Assay has demonstrated strong analytical validity and consistent performance across a series of analytical verification assessments, however evidence supporting this claim was not supplied. The application did not consider sensitivity and specificity (analytical validity), or test-retest reliability.

The application acknowledged that there are differences between CLDN18.2 antibody assays for immune cell staining, and it is important that the antibody / test being used to assess CLDN18.2 status is aligned to the drug being considered. The application stated that the VENTANA CLDN18 (43-14A) RxDx Assay and CLDN18.2 expression ≥75% cut point should be used to determine eligibility for zolbetuximab. However, the applicant proposed MBS item descriptor, informed by the applicant's advisory board, did not specify the test platform or threshold criteria for CLDN18.2 positivity.

There are a range of available IHC tests for CLDN18.2 antibodies. The applicant referenced a global ring study (Jasani et al. 2024) which compared three CLDN18 IHC antibodies (Ventana, Novus and LSBio) processed on three different platforms (Ventana BenchMark, Dako Autostainer Link 48, and Leica Bond). The Ventana antibody (only processed on the Ventana platform) and LSBio antibodies processed on the Dako and Leica platforms demonstrated good-to-excellent levels of concordance measured by the Cohen's Kappa coefficient. However, the Novus antibody showed a high level of variability compared to the reference Ventana method, and failed to meet the study defined threshold for accuracy and sensitivity when used on either the Ventana, Dako or Leica platform (Cohen's Kappa coefficient of 0.50, 0.52 and 0.61 respectively); these comparisons are shown in Table 3 below. Additional diagnostic CLDN18.2 IHC kits outside of this ring study are available, for example as sold by MEDx (MEDx 2024).

Table 3 Comparison of global laboratory antibody and platform combinations performance with the reference Ventana method

Comparison of global laboratory antibody and platform combinations performance with the reference Ventana method

Antibody Platform	Precision			Accuracy			Sensitivity			Specificity			Cohen's Kappa coefficient		
	Ventana	Novus	LSBio	Ventana	Novus	LSBio	Ventana	Novus	LSBio	Ventana	Novus	LSBio	Ventana	Novus	LSBio
Ventana	0.93	0.92	0.83	0.9	0.74	0.85	0.84	0.55	0.87	0.95	0.95	0.83	0.78	0.50	0.68
Dako		0.86	0.93		0.76	0.92		0.6	0.91		0.9	0.93		0.52	0.84
Leica		0.85	0.85		0.8	0.86		0.72	0.85		0.88	0.86		0.61	0.73

Source: Table 3, p 8 (Jasani et al. 2024)

PASC confirmed that the Ventana® CLDN18 (43-14A) RxDx Assay used in the key trials represented the clinical utility standard. PASC and the applicant agreed that this is the most common IHC platform used in Australia noting that there are other relevant IHC platforms and CLDN18.2 antibodies available. The current application is agnostic to IHC platform and CLDN18.2 antibody. The Department advised that the assessment report should include a comparison of the analytical performance between the clinical utility standard and other IHC platform and CLDN18.2 antibody combinations, as per MSAC guidelines (Technical guideline 2.4).

Outcomes

Test-related outcomes

Safety outcomes: adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing.

Diagnostic performance:

- sensitivity and specificity
- test failure rate
- evidence of stability of proteins in archival tissue
- Heterogeneity within tissue samples
- evidence of stability in CLDN18.2 status over time
- assessment of extent of and implications of discordances between Australian IHC testing and clinical utility standard
- test-retest reliability.

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

Safety outcomes: 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:

- 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:

- cost of testing per patient with 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.

PASC confirmed that the outcomes listed in the PICO were appropriate.

In their response to the pre-PASC PICO, the applicant considered it is unnecessary to measure re-biopsy rates and test turn-around time, considering the revised proposal for parallel IHC HER2 and CLDN18.2 testing. The applicant supported the argument by stating that most patients will have recent tissue samples available or very recent archival material, noting that archival tissue can be used for patients with disease relapse. *Post-PASC advice confirmed that it is not necessary to measure re-biopsy rates and test turnaround times given that these measures are likely going to be very small and therefore of limited significance.*

The applicant and PASC discussed the assessment questions included in the PICO summary box. In their pre-PASC response, the applicant considered the three questions listed below to be unnecessary. PASC considered the second question on prognostic value may be unnecessary, while retaining the first and third assessment questions. PASC also noted the applicant's decision on whether to present information in the assessment report to address the question on prognostic value should be informed by the requirements outlined in the PBAC and MSAC guidelines on developing an assessment report for codependent technologies.

1. *Does testing for CLDN18.2 predict a treatment effect modification with zolbetuximab?*
2. *Is there prognostic value in CLDN18.2 expression in G/GOJ adenocarcinoma, and how may this be considered while evaluating the clinical efficacy of zolbetuximab?*
3. *What are the potential costs and cost offsets associated with disease management arising from the listing of CLDN18.2 testing?*

Assessment framework (for investigative technologies)

A linked evidence approach is the most appropriate as there is unlikely to be direct evidence of the impact of claudin testing on health outcomes. An assessment framework linking claudin testing to relevant health outcomes is presented in Figure 1.

Questions relevant to this assessment framework are as follows:

1. Does the use of claudin testing in place of no testing result in the claimed noninferior health outcomes?
2. What is the accuracy of the proposed testing? What are the implications of discordances occurring between the proposed testing procedure and the clinical utility standard?
3. Does the availability of new information (claudin status) from claudin testing lead to a change in management of the patient?

4. Do the differences in the management derived from claudin testing result in the claimed noninferior health outcomes (OS, HRQoL)?
5. Do the differences in the management derived from the proposed test, relative to the comparator (e.g. differences in treatment/intervention), result in the claimed intermediate (PFS, CR, ORR) outcomes?
6. Is the observed change in intermediate outcomes (PFS, CR, ORR) associated with a concomitant change in the claimed health outcomes (OS, HRQoL), and how strong is the association?
7. What are the adverse events associated with claudin testing compared to a no testing strategy?
8. What are the adverse events associated with treatment with zolbetuximab and other alternative treatments?

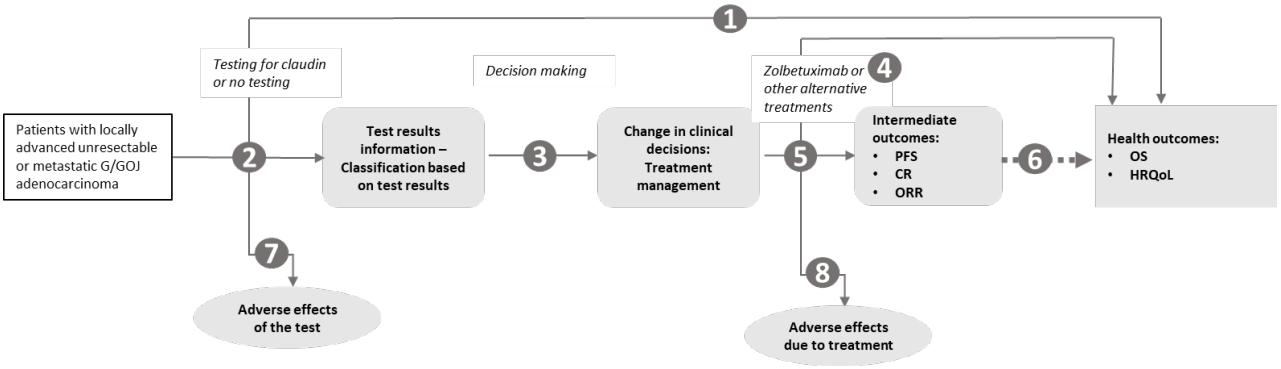


Figure 1 Generic assessment framework showing the links from the test population to health outcomes

CR = complete response; G/GOJ = gastric/gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate health outcomes to final health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment.

PASC confirmed that the assessment framework was appropriately described in the PICO.

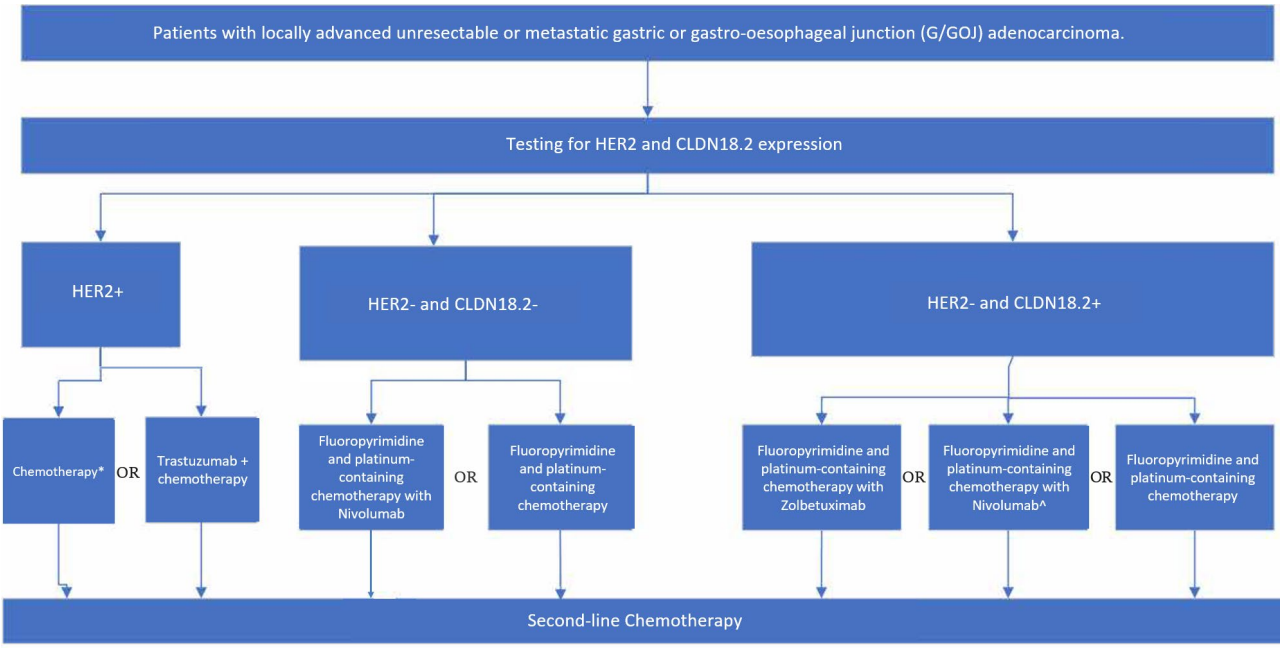
Clinical management algorithms

The application initially proposed all patients with tumours which are HER2-negative would have a CLDN18.2 test performed; based on the result of this test, patients may receive platinum plus fluoropyrimidine-containing chemotherapy (PF chemo) ± nivolumab OR ± zolbetuximab. In its pre-PASC response, the applicant subsequently proposed a revised treatment algorithm proposing that HER2 and CLDN18.2 testing occur in parallel (Figure 3 below).

PASC accepted the updated clinical algorithm proposed by the applicant. PASC also considered nivolumab would be replaced by zolbetuximab, not displaced to later lines. If patients had tumours which are HER2-negative and CLDN18.2+, there is a choice between treatment options (which may include nivolumab or zolbetuximab in combination with chemotherapy, or chemotherapy alone); a range of factors may

influence this decision, including clinician prescribing preferences and patient factors (such as relative or absolute contraindications for either nivolumab or zolbetuximab).

Figure 1 Applicant's revised future treatment algorithm



Source: Provided by the applicant. Figure updated with minor editorial corrections.

Assuming the clinical claim of noninferior clinical efficacy of nivolumab and zolbetuximab is accepted by clinicians, a decision node to determine which patients may be best suited to receive zolbetuximab instead of nivolumab forms a crucial step in the treatment algorithm. Therapeutic decision-making is complex, as clinicians tailor treatments for each patient (Pavlakis et al. 2022); clinician preference, and a range of patient factors may be considered to determine which patients may receive nivolumab versus zolbetuximab, including:

- patient characteristics, comorbidities, and concomitant medications
- prior therapies
    - For example, the subgroup of patients who were diagnosed with early-stage disease, received nivolumab as adjuvant treatment for Stage II or III disease (PBS Authority code 13240W), and have subsequently relapsed would be ineligible for nivolumab in the locally advanced unresectable/metastatic disease setting. It would be reasonable to expect all of these patients who are able to receive zolbetuximab in the unresectable/metastatic HER2-negative, CLDN18.2+ setting would do so, given the superior efficacy of zolbetuximab + PF chemotherapy compared to placebo + PF chemotherapy, as shown in the key trials SPOTLIGHT and GLOW. These patients represent an important consideration for the applicant's cost-minimising approach, as they may be prescribed zolbetuximab.
- the comparative safety profiles of zolbetuximab and nivolumab
- programmed death/ligand-1 (PD-L1) combined positive score (CPS); it is well established that clinical effectiveness (e.g. overall survival) of immune checkpoint inhibitor therapy is positively correlated with CPS (Schoemig-Markiefka et al. 2021). For nivolumab, the key trial (CheckMate

649) demonstrated that CPS <5 was a statistically significant treatment effect modifier, suggesting patients whose tumours had a CPS <5 may have a different response to nivolumab compared to patients whose CPS was ≥5 (nivolumab Public Summary Document, PBAC Meeting November 2021 with March 2022 Addendum). Currently, nivolumab's PBS listing is agnostic to PD-L1, and as it is the only available add-on therapy to chemotherapy in this patient population, PD-L1 testing is unnecessary. However, clinicians may consider PD-L1 CPS score when making treatment decisions with their patients if the future treatment landscape presents an option to treat with either an immune checkpoint inhibitor or zolbetuximab. PD-L1 IHC testing is not MBS listed for the proposed population. MSAC has previously queried the analytical performance and predictive value of PD-L1 IHC testing to identify patients who may benefit from PD-L1 checkpoint inhibitors (MSAC 2022).

Proposed economic evaluation

The applicant's proposed clinical claim is for noninferiority considering the entire pathway, not only the test component. The application claimed the proposed intervention (CLDN18.2 test plus zolbetuximab) is noninferior compared to no testing plus nivolumab. The exact clinical claim proposed in the application is: "Ventana® CLDN18 (43-14A) RxDx Assay plus treatment: zolbetuximab is that it is noninferior to comparator: no testing of CLDN18.2 plus nivolumab."

There is no direct evidence comparing nivolumab versus zolbetuximab. In addition, there is no evidence for nivolumab in patients with tumours found to be CLDN18.2+. During the pre-PASC teleconference, the applicant stated that the need for an indirect comparison is being considered noting that exchangeability issues may arise given the differences in patient populations, which include patients with tumours found to be CLDN18.2+ versus all patients without distinction in CLDN18.2 status. In the absence of direct evidence, the applicant may consider examining the prognostic value of CLDN18.2 expression and biological plausibility to explain the difference in effectiveness of nivolumab between patients with tumours found to be CLND18.2+ and patients with tumours found to be CLDN18.2-. In their pre-PASC response, the applicant noted there is no prognostic value of CLDN18.2 expression in G/GOJ adenocarcinoma. However, evidence on the prognostic value of CLDN18.2 expression in patients with G/GOJ cancer is uncertain (Lu et al. 2020) and it would be informative to consider this in the co-dependent technology application to PBAC and MSAC.

Based on the applicant's clinical claim of noninferiority, a cost-minimisation analysis (CMA) would be appropriate. If the clinical claim during the assessment is found to differ from that proposed, Table 4 provides a guide for determining which type of economic evaluation is appropriate.

Table 4 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety-	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC confirmed that a cost-minimisation analysis would be an acceptable approach based on the applicant's clinical claim of non-inferiority. As the uptake rate of zolbetuximab in patients whose tumours were CLDN18.2+ may be initially low, it is important to consider redundancy of CLDN18.2 testing (i.e. intention is to use a treatment other than zolbetuximab irrespective of test outcome) in the economic analysis and costing.

PASC considered that the clinical claim should more accurately be CLDN18.2 test plus zolbetuximab (in combination with chemotherapy) is noninferior compared to no testing plus nivolumab (in combination with chemotherapy).

Proposal for public funding

Currently there is no existing MBS item for CLDN18.2 testing. The applicant proposed a new MBS item for the CLDN18.2 assay. The proposed item descriptor in the application is presented in Table 5. During the PICO development process the applicant provided several different MBS item descriptors. The latest item descriptors provided by the applicant in their pre-PASC response are presented in Table 6 and Table 7.

None of the proposed MBS item descriptors specify which antibody and testing platform(s) can be used. In addition, the alternative MBS item descriptors suggested by the applicant (Table 6, Table 7) do not specify threshold values to define CLDN18.2 positivity; this may lead to inconsistent thresholds in Australian practice (discussed in 'Intervention' above). This also suggests that the testing is not restricted to the use of the Ventana® platform.

The following issues were identified with the latest item descriptors (Table 6 and Table 7):

- While Option 1 (Table 6) outlined the purpose of testing as access to zolbetuximab under PBS, the Option 2 (Table 7) outlined a more generic purpose (i.e. access to treatments under PBS) and removed the reference to zolbetuximab.
- The two options removed the word 'gastric' from the item descriptors and narrowed down the testing population to only those patients diagnosed with locally advanced unresectable or metastatic GOJ adenocarcinoma.
- Both the options removed the word 'HER2 negative' from the item descriptors. This suggests CLDN18.2 testing will be done in all patients with locally advanced unresectable or metastatic GOJ adenocarcinoma irrespective of HER2 status. It also suggests that CLDN18.2 testing is done in parallel to HER2 testing instead of being sequential testing (i.e., HER2 testing followed by CLDN18.2 testing). Considering patients with GC are also tested, this will increase the need for testing which will impact the applicant's cost-minimisation approach.
- Both the options changed the wording from 'tumour tissue' to 'biopsy material'. The rationale behind this change is unclear.
- Both options refer to CLDN18 expression rather than 'positive' and/or a threshold to define positivity.

The latest item descriptors provided by the applicant (Table 6 and Table 7) proposed to remove the 'Applicable only once per lifetime' and 'The service is requested by an oncologist' from the item descriptors. A certified pathologist would be responsible for conducting the testing and reporting of results. It is proposed that CLDN18.2 testing be eligible to be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS.

The proposed fee for the test was estimated to be $550.00 by the applicant. During the pre-PASC teleconference, the applicant acknowledged that the price was high, and may need further consideration. The applicant indicated that the price would not be as low as $74.50 (current IHC fee, MBS Item 72848) but not as high as $550 (the current proposed fee). The applicant is still working on determining the price and is conducting a bottom-up desk-based analysis to determine the price. During the pre-PASC teleconference, it was clarified that the process for running the CLDN18.2 test is similar to the HER2 and PD-L1 IHC testing - it requires a two-part scoring algorithm, with manual review of slides (that are stained) and application of an agreed algorithm. As an additional reference, the fee for generic IHC testing (MBS item 72846) is $59.60

Table 5: Item descriptor initially proposed by the applicant in their application

Category 6 – PATHOLOGY SERVICES
MBS item *XXXX Immunohistochemical examination of tumour tissue from a patient diagnosed with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 negative gastric or gastro-oesophageal junction adenocarcinoma to determine the requirements relating to CLDN18.2 expression (tumour cells ≥75%) for access to zolbetuximab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. The service is requested by an oncologist. Applicable only once per lifetime.
Fee: $550.00

Source: HPP200118 - CLDN18.2 PICO Set Document_v2.2.docx received as part of the application.

Table 6: Item descriptor proposed by the applicant in their pre-PASC response – Option 1

Category 6 – PATHOLOGY SERVICES
MBS item *XXXX Immunohistochemical examination of biopsy material from a patient with locally advanced unresectable or metastatic gastro-oesophageal junction adenocarcinoma to determine the requirements relating to CLDN18 expression for access to zolbetuximab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Fee: $TBD

Source: Applicant pre-PASC response.

Table 7: Item descriptor proposed by the applicant in their pre-PASC response – Option 2

Category 6 – PATHOLOGY SERVICES
MBS item *XXXX Immunohistochemical examination of biopsy material from a patient with locally advanced unresectable or metastatic gastro-oesophageal junction adenocarcinoma to determine the requirements relating to CLDN18 expression for access to treatments under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Fee: $TBD

Source: Applicant pre-PASC response.

As CLDN18.2 testing is now proposed to occur in parallel to HER2 testing, PASC confirmed that 'human epidermal growth factor receptor 2 negative' (HER2-negative) can be removed from the proposed item descriptor. PASC considered it unnecessary to compare the cost effectiveness of sequential versus parallel testing, given that only parallel testing is proposed.

PASC noted the applicant's pre-PASC response proposed using the term "CLDN18 expression" instead of specifying 'positive' and/or a threshold to define positivity. The applicant's pre-PASC response suggested that as more studies on CLDN18.2 testing and targeted therapies become available, the optimal threshold for positivity may change. Using a fixed threshold in the MBS item description would not allow for flexibility to accommodate evolving evidence or future applications of the test. PASC confirmed using the term "CLDN18 expression" without the term 'positive' or the specification of a threshold is acceptable.

PASC noted the applicant's pre-PASC response proposed replacing the wording 'tumour tissue' with 'biopsy material'. PASC considered 'tumour tissue' to be the preferred terminology as clinicians require information specifically on the tumour tissue, rather than an undefined biopsy specimen which might be from non-tumour tissue.

PASC noted that the applicant omitted the word 'gastric' from the item descriptor, limiting the application to patients with gastro-oesophageal junction tumours only. During the PASC meeting, the applicant confirmed this was not intentional, but an error and the item descriptor should include the word 'gastric', as it sought to include patients with gastric adenocarcinoma, in addition to patients with gastro-oesophageal junction adenocarcinoma.

PASC considered that the proposed descriptor could be 'future-proofed' by replacing the specific reference to zolbetuximab wording with 'access to a relevant treatment listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled'.

PASC considered that the treating clinician (oncologist) would have the necessary clinical information to determine if CLDN18.2 testing was required along with the ability to interpret the test result to inform any change in patient management. As such, PASC considered the treating clinician would be best placed to request the CLDN18.2 test and therefore considered that the test should be clinician-determinable.

PASC considered the risk of leakage to be low. PASC confirmed it is reasonable to remove the 'Once per lifetime' restriction, in case of likely rare scenarios where an additional biopsy/test is required.

PASC considered the proposed item fee of $550 is high and inadequately justified, given that the fee for generic MBS item 72846 for IHC examination is $59.60 and that for MBS Items 72848 and 72814 (IHC testing to determine HER2 and PD-L1 status respectively) is $74.50. During the PASC meeting, the applicant confirmed a reduced item fee will be finalised and incorporated in the applicant developed assessment report (ADAR), as they are in consultation with Roche Diagnostics and the RCPA to determine an appropriate fee for CLDN18.2 testing. PASC raised the importance of keeping any out-of-pocket costs to a minimum in the consideration of the revised item fee. The applicant noted there would be no anticipated out-of-pocket costs for patients.

Following the PASC meeting, the evaluation group updated the MBS item descriptor to align with PASC advice (Table 8).

Table 8: Proposed item descriptor based on PASC advice

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 to determine the requirements relating to CLDN18 expression for access to a relevant treatment listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. The service is requested by an oncologist.
Fee: $TBD

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Summary of public consultation input

PASC noted and welcomed consultation input from two *organisations. The two organisations that submitted input were:*

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

There was no input from consumers or consumer organisations. The consultation feedback received was all supportive of public funding for IHC testing for Claudin 18 expression in patients with G/GOJ cancers, to determine eligibility for PBS subsidised zolbetuximab treatment.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included, proposed service ability to inform clinicians to provide the best possible treatment to targeted population of patients.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback strongly agreed with population and comparator.

The consultation feedback strongly agreed with the clinical claim with the RCPA noting, test should be pathologist determinable.

Cost information for the proposed medical service

The consultation feedback received from both organisations strongly supported the proposed service descriptor (as per the application form) and $550 fee for the test. The RCPA indicated that all semiquantitative IHC assays that are used to determine access to a specific drug require advanced level of validations, pathologist training and ongoing quality control/quality assurance to ensure they are being performed correctly. The RCPA further noted that if the labs are using the IHC antibody for an in house developed IVD, the requirements for assay validation are more stringent and costly than those of diagnostic antibodies.

Consumer Feedback

PASC noted that the consultation input from Australian Pathology and the RCPA wase supportive of the proposed service and the proposed MBS fee of $550. PASC further noted that the RCPA considered that the test should be pathologist determinable.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR (integrated codependent submission).

Applicant Comments on Ratified PICO

Applicant had no comments.

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