Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1750 – Testing of tumour tissue to detect IDH1 mutations in patients with cholangiocarcinoma to determine eligibility for ivosidenib on the Pharmaceutical Benefits Scheme

Applicant: **Servier Laboratories (Aust.) Pty. Ltd.**

Date of MSAC consideration: **1-2 August 2024**

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 *isocitrate dehydrogenase 1* (*IDH1*) testing for the evaluation of Tier I IDH1 p.R132X variants for the determination of patient eligibility for treatment with ivosidenib in patients with cholangiocarcinoma (CCA) and

- Pharmaceutical Benefits Scheme (PBS) General Schedule, Authority Required - listing of ivosidenib for the treatment of locally advanced or metastatic cholangiocarcinoma in patients who have evidence of an *IDH1* variant and who have previously progressed on systemic therapy.

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 deferred its advice on the public funding of *isocitrate dehydrogenase 1* (*IDH1*) genetic testing to detect variants that provide ivosidenib access under the Pharmaceutical Benefits Scheme (PBS) in patients with cholangiocarcinoma. MSAC acknowledged that patients with cholangiocarcinoma typically have a poor prognosis, and that there was a high clinical need for treatments for this condition. MSAC considered the testing was safe, the cost to the MBS was acceptable, and if it provided access to ivosidenib on the PBS then this test would improve health outcomes for the subset of patients with cholangiocarcinoma who harbour an *IDH1* variant. However, MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) had not recommended listing ivosidenib on the PBS, primarily on the basis that the incremental cost-effectiveness ratio (ICER) was high. MSAC foreshadowed that it would expeditiously reconsider this testing if the PBAC recommended ivosidenib for patients with cholangiocarcinoma in whom an *IDH1* variant is detected.

Consumer summary

This was an application from Servier Laboratories Australia Pty. Ltd. requesting Medicare Benefits Schedule (MBS) listing of testing for genetic variants in the *IDH1* gene in patients with cholangiocarcinoma. The aim of this genetic testing would be to show which patients would be eligible for a medicine called ivosidenib on the Pharmaceutical Benefits Scheme (PBS). Ivosidenib is not yet listed on the PBS, so this was a codependent application that proposed public funding of both the test and the medicine.

Cholangiocarcinoma is cancer of the bile ducts, which are a group of thin tubes starting inside the liver that carry bile from the liver and gallbladder into the intestine. Cholangiocarcinoma is rare and usually patients with it have very poor prognosis, with relatively short duration of survival after diagnosis. The applicant proposed ivosidenib be funded for patients with locally advanced or metastatic cholangiocarcinoma (metastatic meaning the cancer has spread beyond where it originated), who have previously tried chemotherapy, and who are found to have a certain type of *IDH1* genetic variant in their tumour. The relevance of *IDH1* genetic variant testing is that presence of *IDH1* variant leads to increased levels of an oncometabolite called D-2-hydroxyglutarate (D2-HG) (a metabolite is a substance generated when cells produce energy and an oncometabolite is a type of metabolite which contributes to the growth of the cancer). Because ivosidenib treats this cancer by reducing abnormal levels of D2-HG it is relevant that the drug is only targeted at people with this genetic variant (hence the importance of I*DH1* testing). MSAC considered there was a strong clinical need for cholangiocarcinoma treatments, as there are currently not many treatment options available to these patients.

The testing for the *IDH1* variant is done in a pathology lab using the same tumour sample that is taken during the biopsy procedure that the patient has done as part of their cholangiocarcinoma diagnosis. Therefore, MSAC advised that adding this testing does not change the safety of the diagnostic process for the patient.

Ivosidenib treatment made a small improvement to the average survival of patients with cholangiocarcinoma whose tumour has an *IDH1* genetic variant, so MSAC considered that *IDH1* testing would improve health outcomes if patients could access ivosidenib on the PBS.

However, the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend listing ivosidenib on the PBS. While the PBAC recognised the clinical need for more treatments for patients with cholangiocarcinoma, and that ivosidenib led to a small survival improvement in patients whose tumours had an *IDH1* variant, the PBAC considered the drug was poor value for money at the price the applicant had proposed, and so did not list it on the PBS.

MSAC therefore deferred its advice on funding *IDH1* testing, because the value of this testing comes from identifying patients who would benefit from ivosidenib if listed on the PBS.

The applicant may be able to address the PBAC's concerns with the drug part of this codependent application relatively quickly. MSAC foreshadowed that it would rapidly reconsider listing *IDH1* genetic testing for patients with cholangiocarcinoma on the MBS if the PBAC recommends listing ivosidenib on the PBS.

Cholangiocarcinoma is rare and not many people would need this testing, so MSAC advised the financial cost of this testing to the MBS would be acceptable.

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

MSAC deferred its advice on funding *IDH1* genetic testing for patients with cholangiocarcinoma. The test was safe and it would have an acceptable financial cost to the MBS. It would improve health outcomes for patients with an *IDH1* genetic variant if it provided access to ivosidenib on the PBS, however the PBAC did not recommend listing ivosidenib. MSAC therefore deferred its advice, but would rapidly reconsider this testing if the PBAC recommends listing ivosidenib on the PBS.

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

MSAC noted that this application from Servier Laboratories Australia Pty. Ltd. was an integrated codependent submission to the MSAC and the PBAC, requesting MBS listing of testing to detect *IDH1* genetic variants in the tumours of adult patients with locally advanced or metastatic CCA who have previously progressed on chemotherapy, and PBS listing of ivosidenib (Tibsovo®) for the treatment of those patients whose tumours are found to have an *IDH1* genetic variant.

MSAC noted that it has not previously considered *IDH1* genetic testing for patients with CCA, but *IDH1* genetic testing is already funded for patients with glioma or glioblastoma: they can currently access *IDH1/2* testing under MBS item 73372, and gene panel testing under MBS item 73429. Other MBS items also provide gene panel testing for the diagnosis and classification of haematological malignancies, which must include genes described in clinical guidelines, and these currently include *IDH1*.

MSAC noted that CCA is rare, comprising about 3% of all gastrointestinal cancers. MSAC noted the median survival of patients diagnosed with CCA or advanced CCA, and considered that patients with CCA typically have a poor prognosis. MSAC acknowledged the significant unmet clinical need for treatments for patients with this rare cancer.

MSAC noted that all consultation feedback received – including from Pancare, the Liver Foundation, the Medical Oncology Group of Australia and the Cholangiocarcinoma Foundation – was supportive of the application.

MSAC noted the population, intervention, comparator and outcome (PICO) that had been ratified by the PICO Advisory Subcommittee, and considered it was appropriate.

MSAC noted the claim of codependence was not explicitly justified in the applicant-developed assessment report (ADAR), but acknowledged there is a biological rationale for the way in which *IDH1* p.R132 gain of function variants alter the behaviour of the *IDH1* gene, resulting in overexpression of the IDH1 enzyme that causes excessive accumulation of the oncometabolite 2-hydroxyglutarate (2-HG). Ivosidenib has been shown to bind to the altered IDH1 enzyme, thus reducing 2-HG levels and consequent oncogenesis. MSAC considered this implied rationale to be reasonable and accepted the claim of codependence.

MSAC noted that the clinical evidence was primarily from the ClarIDHy trial, a multicentre, randomised, double-blinded, placebo-controlled phase 3 study.

MSAC noted that no test-related adverse events were reported in the ADAR, but because testing for *IDH1* variants would be performed on the same tumour tissue used to histologically diagnose CCA, MSAC considered there to be no additional adverse events expected from this testing. MSAC noted that testing at the point of diagnosis should allow efficient use of tumour tissue. MSAC considered that the likelihood of requiring a re-biopsy for genetic testing was negligible. Overall, MSAC advised this testing was comparatively safe.

MSAC noted Kaplan-Meier plots of overall survival (OS) in the intention-to-treat population showed a benefit for people treated with ivosidenib (median OS = 10.3 months [7.8–12.4 95% confidence interval (CI)]) compared to placebo (median OS = 7.5 months [4.8–11.1 95% CI]). Median OS for placebo adjusted for rank-preserving structural failure time (RPSFT) was even lower at 5.1 months (3.8–7.6 95% CI). MSAC considered the evidence demonstrated that treating patients who have an *IDH1* variant with ivosidenib resulted in a modest improvement to survival, and so advised the testing would be comparatively effective if it provided access to ivosidenib.

However, MSAC noted the PBAC had not recommended PBS listing of ivosidenib at its July 2024 meeting, due to the high incremental cost-effectiveness ratio (ICER) at the proposed price and what PBAC considered to be optimistic assumptions in the economic model. MSAC considered that it could not support this testing without PBAC having first recommended PBS listing of ivosidenib, as

the clinical utility of *IDH1* genetic testing relies on it providing access to ivosidenib for the subset of patients found to have a relevant genetic variant.

MSAC noted the economic evaluation was a cost-utility analysis and a cost-effectiveness analysis with evidence derived from the ClarIDHy trial. The ADAR assumed the test had 100% specificity and sensitivity with an *IDH1* variant prevalence of 9.15%, which MSAC accepted. At the proposed fee of $340, MSAC noted the ADAR had estimated the cost to identify one patient with an *IDH1* mutation was approximately $3,717, and the incremental cost-effectiveness ratio was $95,000<$115,000 per quality-adjusted life-year (QALY). MSAC considered the cost per patient was underestimated, as it included patients who did not progress and those who were too frail for treatment, but these factors did not have a significant impact on the ICER. MSAC noted PBAC had considered the economic model made optimistic assumptions, and had advised the ICER was too high. MSAC noted that the main driver of the ICER was the cost of ivosidenib treatment, and that the costs of testing, disease management, adverse events management and terminal care costs were minor cost contributors. MSAC also noted it is current clinical practice for *IDH1* testing to be performed at diagnosis, and that this was appropriately accounted for in the economic and financial assessments.

MSAC noted that the financial cost to the MBS was $0<$10 million in Year 1, increasing slightly to $0<$10 million in Year 6, assuming 85% benefit. MSAC also noted the commentary had raised that the proposed MBS electrocardiogram costs for treatment monitoring were likely overestimated, and the applicant had accepted this in its pre-ESC response. MSAC noted ESC's concern about possible diagnostic expansion leading to *IDH1* testing intended for patients with CCA also being conducted in patients with primary distal common bile duct or head of pancreas, and metastatic pancreatobiliary cancer or carcinoma of unknown primary site. MSAC noted the pre-MSAC response argued that this was unlikely, as a diagnosis of CCA is required to have occurred before genetic testing of the tumour tissue. MSAC agreed with ESC that these cancers had similar profiles to CCA, and noted that *IDH1* variants are more common in intrahepatic CCA than in extrahepatic CCA. MSAC considered that, even if there was leakage through diagnostic expansion, the additional service volume would be extremely small. MSAC considered it would be appropriate for all patients with a tumour in their bile ducts to receive this testing (including when it is uncertain whether the CCA is the primary tumour), and that this would not have any material effect on the financial cost or the cost-effectiveness of testing. Overall, MSAC advised the financial cost of *IDH1* testing to the MBS was acceptable. However, given the remaining uncertainty around test volumes, MSAC considered if it were to support this testing, it would be appropriate to review service volumes following implementation. MSAC considered implementation issues would be unlikely for this testing as similar testing is already being done for other cancers.

MSAC noted ESC's revisions to the proposed MBS item descriptor and ESC's advice that in contemporary clinical practice a gene panel test is used. MSAC considered the method-agnostic description of testing for *IDH1* variant status was appropriate and would not preclude claiming this service when a gene panel was used. MSAC considered the proposed fee of $340 was appropriate, as this is the same fee for existing MBS-listed *IDH1/2* genetic testing. MSAC noted the proposed once per lifetime restriction, and considered this to be reasonable given the typically poor prognosis of patients with CCA. MSAC also agreed with ESC in considering that it was unnecessary for the MBS item descriptor to specify the test was for "p.R132X tier I" variants, as the MBS item descriptor only needs to describe what the test is to examine (in this case, *IDH1* variant status), rather than the test result required to grant PBS access. MSAC noted the applicant had proposed the item descriptor state that the test provide access to ivosidenib specifically, but MSAC considered that referring instead to "a relevant treatment under the Pharmaceutical Benefits Scheme" would futureproof the descriptor. MSAC considered that it was ideal to align comparable wording between different MBS item descriptors where appropriate, and noted "a relevant treatment" would align with its previously advised wording under MSAC application 1765. MSAC considered the test should be pathologist-determinable, as previous testing as part of tissue examination and cytology MBS items would be performed to provide a diagnosis of CCA and so determine eligibility for molecular testing.

Reflecting the above, the revised MBS item descriptor that MSAC considered would be appropriate for its future reconsideration of this testing if PBAC supports ivosidenib, is below (Table 1).

Table 1 MSAC's revised MBS item descriptor

Category 6 – Pathology Services Group P7 – Genetics
XXXXX Detection in tumour tissue of *isocitrate dehydrogenase 1 (IDH1)* variant status, in a patient with histologically confirmed cholangiocarcinoma, to determine access to a relevant treatment under the Pharmaceutical Benefits Scheme. Applicable only once per lifetime
Fee: $340 Benefit: 75% = $255.00 85% = $289.00

Overall, MSAC considered *IDH1* genetic testing was comparatively safe, would have an acceptable financial cost to the MBS, and that if it provided access to ivosidenib on the PBS then it would improve health outcomes for the nearly 10% of patients with cholangiocarcinoma who harbour an *IDH1* variant. However, as the PBAC had not recommended listing ivosidenib on the PBS, MSAC deferred its advice. MSAC noted the PBAC considered its concerns could be addressed in an early re-entry resubmission, and MSAC foreshadowed it would expeditiously reconsider this testing if the PBAC recommended ivosidenib.

MSAC considered that its reconsideration of *IDH1* testing for patients with cholangiocarcinoma may have implications for other MSAC applications. If *IDH1* testing is supported by MSAC before it considers other applications, *IDH1* testing may form part of the comparator in an assessment of gene panel testing for patients with CCA, for example under *MSAC Application 1779 – Testing to detect FGFR2 fusion or rearrangement in patients with locally advanced or metastatic cholangiocarcinoma, to determine PBS eligibility for futibatinib*[1].

4. Background

This was the first submission for *IDH1* variant testing for cholangiocarcinoma (CCA) to the MSAC, and the first submission for ivosidenib for CCA to the PBAC.

MSAC has previously considered *IDH1* testing for glioma and glioblastoma (MSAC applications 1527[2] and 1709[3]) and as part of a panel test for variants associated with haematological malignancies (MSAC application 1684[4]), which led to the creation of MBS items 73372, 73429, 73445, 73446, 73447 and 73448.

5. Prerequisites to implementation of any funding advice

The test is a Class 3 in-house *in vitro* diagnostic (IVD) and therefore does not need to be included in the ARTG[5].

The ratified PICO confirmation stated that laboratories who offer the test will need to participate in the relevant Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program or a similar external quality assurance program.

[1] MSAC Application 1779, available at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1779-public
[2] MSAC Application 1527, available at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1527-public
[3] MSAC Application 1709, available at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1709-public
[4] MSAC Application 1684, available at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1684-public
[5] Therapeutic Goods Administration (2018). *Regulatory requirements for in-house IVDs*. Version 2.2. Australian Department of Health

6. Proposal for public funding

The proposed MBS listing, consistent with the ratified PICO confirmation (except for *'isocitrate dehydrogenase 1 (IDH1)'* which was omitted in the submission), is shown in Table MSAC. 1.

The proposed item is method-agnostic, although it is anticipated that Australian laboratories are most likely to use either Sanger sequencing, pyrosequencing or Next Generation Sequencing (NGS) technologies for molecular testing.

There is a similar MBS listing of *IDH1* testing of tumour tissue from patients diagnosed with gliomas (MBS item 73372), but the proposed item is the first for testing patients with cholangiocarcinoma. The proposed fee is identical to the current MBS item 73372 for *IDH1/2* variant testing.

Table MSAC. 1 Proposed MBS item for *IDH1* status testing

Category 6 – PATHOLOGY SERVICES
XXXXX Detection in tumour tissue of isocitrate dehydrogenase 1 (*IDH1*) p.R132X tier I variant status, in a patient with histologically confirmed cholangiocarcinoma, to determine access to an isocitrate dehydrogenase 1 inhibitor under the Pharmaceutical Benefits Scheme (PBS). Applicable only once per lifetime
Fee: $340 Benefit: 75% = $255.00 85% = $289.00

Source: Table 1-7, p46 of the submission

'*IDH1* p.R132X tier I variant status' is intended to refer to a genetic variant in the deoxyribonucleic acid (DNA) sequence at codon 132 of the *IDH1* gene, such that the resultant amino acid substitution encodes a 'gain-of-function' IDH1 protein (IDH1 p.R132X). This includes genetic variants encoding IDH1 p.R132C, p.R132G, p.R132H, p.R132L, and p.R132S, as well as other amino acid substitutions at p. R132 leading to a 'gain of function' oncogenic IDH1 protein. Throughout this document, "*IDH1* testing" refers to genetic testing to identify a tier I *IDH1* genetic variant that encodes a gain of function amino acid substitution at codon 132 of the IDH1 protein.

The use of the item is restricted to laboratories holding National Association of Testing Authorities (NATA) accreditation.

The commentary noted that there are no restrictions on the proposed population to be tested, other than having histologically confirmed cholangiocarcinoma, and the testing was proposed by PASC to be pathologist-determinable. PASC noted that although the item descriptor mentions testing of tumour tissue, this is understood to also include cytology samples.

PASC considered that, based on glioma biomarker stability data, the frequency restrictor of not more than once per lifetime for *IDH1* testing, appeared appropriate. The commentary noted that there is a limited volume of evidence that additional *IDH1* or *IDH2* variants may be acquired and likely responsible for resistance to ivosidenib. The commentary noted that no monitoring for resistant variants was proposed.

7. Population

The population proposed to be eligible for the test are those with histologically confirmed CCA, regardless of stage or subtype. This approach, combined with the ability for the pathologist to reflexively test for *IDH1* gene variants following confirmation of cholangiocarcinoma, allows the diagnostic process to be streamlined, reducing the requirement for block retrieval and making more efficient use of the tumour tissue.

If a tier I IDH1 p.R132X variant is identified and the patient also meets other criteria, then they may receive ivosidenib. The additional criteria are:

- having locally advanced or metastatic cholangiocarcinoma,
- having received prior systemic therapy (typically gemcitabine or fluorouracil-based treatment),
- a World Health Organization (WHO) performance status of 2 or less, and
- not receiving other PBS-subsidised treatment for cholangiocarcinoma.

When the *IDH1* gene has a p.R132X variant, it creates IDH1 enzymes that generate increased levels of the oncometabolite D-2-hydroxyglutarate (D2-HG), which interferes with cellular metabolism and epigenetic regulation, contributing to oncogenesis. The D2-HG also inhibits alpha-ketoglutarate dependent dioxygenases such as histone and DNA demethylases. This impairs cell differentiation and further contributes to oncogenesis.

Ivosidenib is a small molecule inhibitor of IDH1*,* interfering with the metabolic pathway to prevent D2-HG accumulation. Pre-clinical studies have demonstrated a dose-dependent reduction in D2-HG levels. The inhibition of histone demethylases means that normal methylation conditions can be restored, which promotes cell differentiation.

The commentary considered the biological rationale for testing for *IDH1* variants as a biomarker for targeted treatment with ivosidenib appeared reasonable.

CCA is a type of biliary tract cancer (BTC) in the epithelial cells lining the biliary tree. These ducts are responsible for transporting bile, a digestive fluid produced in the liver, to the small intestine. The two main types of CCA are intrahepatic CCA (iCCA, which originates within the bile ducts inside the liver), and extrahepatic CCA (eCCA, which develops in the distal portion of the bile duct, close to where it joins the pancreatic duct before entering the small intestine). In people with iCCA, the prevalence of *IDH1* variants in their tumours is 13%-20%, and in eCCA, the prevalence of *IDH1* variants is 0.80%[6]. The weighted prevalence is 9.15%. This was based on a systematic review of 46 studies of cohorts from the United States, Europe, Asia and South America. An independent search found no data on the prevalence of *IDH1* variants in Australian cases of CCA. In the absence of Australian data, this review provides a reasonable estimate of the prevalence of *IDH1* variants, that is likely to be generalisable to the target population.

The current clinical management algorithm starts with patients with histologically confirmed CCA, which is then classified as early stage/resectable, or locally advanced or metastatic CCA. In those who are diagnosed or progress to locally advanced or metastatic disease, the first-line treatment is systemic therapy, predominantly chemotherapy with gemcitabine plus cisplatin, with addition of durvalumab since December 2023 in accordance with the latest National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines. On disease progression, patients may then either receive the combination of folinic acid, fluorouracil and oxaliplatin (FOLFOX) or palliative care. If patients receive second-line FOLFOX and have disease progression, they would then receive palliative care/no treatment.

The proposed clinical management algorithm differs from the current management algorithm at the point of diagnosis of CCA. At this point, *IDH1* variant testing is proposed to occur, although the test results would only influence management for those who have, or progress to having, locally advanced or metastatic disease, and who have had systemic therapy, and disease progression. At this point, ivosidenib is an alternative treatment option to FOLFOX or palliative care. Likewise, for

[6] Boscoe AN, et al (2019). Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol*. 2019;10(4):751-65.

those who have received FOLFOX and have disease progression, ivosidenib is proposed as an alternative to palliative care.

The commentary noted that the Applicant Developed Assessment Report (ADAR) was consistent with the ratified PICO confirmation regarding the population to be tested and treated.

8. Comparator

The comparator to *IDH1* testing in the submission and ratified PICO confirmation is no testing. As the comparator treatment is provided to an untargeted population, the commentary considered it was appropriate.

The primary comparator for ivosidenib in the submission is proposed to be palliative care, with FOLFOX as a secondary comparator. The commentary noted that this was justified based on articles reporting on practice prior to 2021, prior to the results of the ABC-06 trial being published. Since 2021, FOLFOX has become the recommended second-line treatment after progression while on first-line systemic therapy[7].

9. Summary of public consultation input

Consultation input was welcomed from one (1) professional organisation, two (2) consumer organisations and four (4) individuals, all of whom were medical specialists.

The organisations that submitted input were:

- Pancare Foundation
- Cholangiocarcinoma Foundation Australia
- Royal College of Pathologists of Australasia (RCPA)

Benefits

- Patients living with cholangiocarcinoma currently have limited first line therapies and subsequent line therapies available for disease recurrence and management, so adding a therapeutic option would be valuable.
- The benefits of second line chemotherapy are modest, and the side effect profile is not well tolerated for many.

1.1 Equity of access for patients unable to afford the test, and testing all patients with cholangiocarcinoma will capture as many patients as possible whose tumours may harbour an *IDH1* variant.

- Testing would enable a more personalised treatment approach.
- Testing at the point of diagnosis, rather than during disease progression, would allow for appropriate treatment to commence sooner.
- Patients would spend less time either as inpatients or outpatients in hospital to receive chemotherapy or palliative treatment or treatment due to side effects of chemotherapy.
- Patients with locally advanced or metastatic cholangiocarcinoma who have the *IDH1* variant and who are treated with ivosidenib experience improved progression-free survival, overall survival and maintenance of quality of life.

[7] Rimini M, et al. (2023). Clinical Outcomes After Progression on First-Line Therapies in IDH1 Mutated Versus Wild-Type Intrahepatic Cholangiocarcinoma Patients. *Target Oncol.* Jan;18(1):139-45

Disadvantages

- If tumour tissue from a patient with cholangiocarcinoma is tested and found to be negative for an *IDH1* variant, the patient, their family and carers, and their treatment team may react negatively to the results.
- There may be challenges in ensuring that the test is accessible to all patients across different regions, especially in remote or underserved areas.
- There may be issues with relevant parties not fully aware of the availability and importance of the *IDH1* test.
- The possibility of false positive or false negative results may lead to inappropriate treatment decisions.
- Costs of implementing and maintaining the testing program.

Additional Comments

Pancare and Cholangiocarcinoma Foundation Australia commented that patient should be supported around the testing, including genetic counselling and psychological support. Patients must also have access to appropriate medical and non-medical interventions.

The RCPA noted that the application mentions the 'tissue' in the item descriptor, and that this could potentially include specimen types unsuitable for genetic testing (such as cytology specimens).

10. Characteristics of the evidence base

Table MSAC. 2 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	☒ k=1 n=383	Low risk of bias (QUADAS 2)	No
Prognostic evidence (longitudinal accuracy)	Comparison of health outcomes in patients receiving *usual care*, conditioned on the presence or absence of biomarker-positive status	☒ k=6 n=1153	Moderate risk of bias (QUIPS)	No
Change in patient management	No evidence supplied	☐ k=0 n=0	-	-
Health outcomes (clinical utility)	As per treatment effect (enriched)	☐ k=1 n=187	Low	Yes
Predictive effect (treatment effect variation)	No evidence supplied (only biological rationale)	☐ k=0 n=0	-	-
Treatment effect (enriched)	Single randomised controlled trial of drug vs placebo in patients that are test positive in both arms	☒ k=1 n=187	Low	Yes
Other Treatment effect compared to secondary comparator	Indirect comparison	☒ k=2 n=349	High (due to transitivity issues)	Sensitivity analysis only

Source:
k=number of studies, n=number of patients.

11. Comparative safety

Adverse events from testing

The commentary noted that no test-related adverse events were mentioned in the submission. If testing for *IDH1* variants is performed on the same tumour tissue used to histologically diagnose CCA, then no incremental adverse events are expected from testing.

The commentary considered testing at the point of diagnosis should allow efficient use of tumour tissue, so the likelihood of requiring a re-biopsy for the purpose of retrieving tumour tissue for genetic testing is negligible.

Adverse events from changes in management

The use of *IDH1* variant testing would result in the majority of those with tier I variants receiving ivosidenib.

Safety data from the ivosidenib key trial showed that, for a median treatment duration of 2.8 months, approximately half (50.4%) of the patients in the ivosidenib arm (not including crossover patients) experienced ≥ Grade 3 treatment-emergent adverse events (TEAEs). Grade 3 or higher grade TEAEs that were most frequently reported (≥ 5%) in patients receiving ivosidenib included: ascites (7.4%), anaemia (6.5%), increased serum bilirubin (5.7%) and hyponatraemia (5.7%). Serious adverse events (SAEs) occurred in 34.1% of patients in the ivosidenib arm. The most common SAEs included pneumonia (3.3%), sepsis (3.3%), ascites (2.4%) and cholangitis (2.4%). TEAEs leading to death occurred in 4.9% of patients in the ivosidenib arm. This compared to 37.3% experiencing ≥ Grade 3 TEAEs in the palliative care arm over a median duration of 1.6 months. Grade 3 or higher grade TEAEs most frequently reported (≥ 5%) in patients receiving palliative care included: hyponatraemia (10.2%), ascites (6.8%), hypophosphataemia (5.1%), and increased blood alkaline phosphatase (5.1%). Serious adverse events (SAEs) occurred in 23.7% of patients in the palliative care arm. The most common SAEs included ascites (3.4%), sepsis (3.4%), hypercalcaemia (3.4%), hyperkalaemia (3.4%), and back pain (3.4%). Other SAEs that occurred in 2 or more ivosidenib patients but not in palliative care patients included hip fracture, vomiting, hyperbilirubinemia, jaundice cholestasis, intestinal obstruction and pleural effusion. No TEAEs causing death occurred in patients receiving palliative care.

Drug-related AEs occurred in 65.9% (81) patients in the ivosidenib arm (not including crossover patients). The most commonly reported (≥ 5%) ivosidenib-related TEAEs included diarrhoea (22.8%), nausea (22.8%), fatigue (17.1%), vomiting (9.8%), decreased appetite (8.9%), headache (8.1%) and prolongation of corrected QT (QTc) interval (6.5%). Ivosidenib-related TEAEs most frequently affected the gastrointestinal system in trialled patients.

The commentary noted that the MSAC Executive advised that the analytical validity of *IDH1* variant testing did not need to be assessed. It indicated that no downstream adverse events resulting from false positives or false negatives are expected.

12. Comparative effectiveness

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

Table MSAC.3 Data availability to inform comparisons

	Ivosidenib	**Comparator drug**
Biomarker test positive	ClarIDHy trial	ClarIDHy trial Prognostic studies
Biomarker test negative	No evidence presented	Prognostic studies

Source: *Developed during the evaluation*

Comparative accuracy/ test performance

The commentary noted that in May 2023, the MSAC Executive advised that it was not necessary to assess comparative analytical performance across the different molecular methods for this application.

The submission still performed a systematic review on the analytical performance of NGS for detecting *IDH1* variants. A single study was identified, which compared one NGS test against the clinical utility standard (another form of NGS test) and also against Sanger Sequencing (see Tables below). There was a high rate of concordance between the testing methodologies, suggesting that the tests used in Australia are likely to detect the biomarker to a similar extent to the test used in the key trial in similar patient groups. The impact of any false positives or negatives is therefore minimal with the use of these test methods. It is noted that the proposed MBS item is method-agnostic and so there is no guarantee that future testing methods would perform as well as these test methods at identifying *IDH1* variants.

Of the 383 samples tested on either NGS test, there were 9 invalid samples (2.3%), of which one (0.3%) could not be retested due to sample availability. The testing was performed as part of the ClarIDHy trial, where testing was performed after disease progression from one or two regimens of therapy for advanced disease. Testing performed at the point of diagnosis may make more efficient use of tumour tissue and may feasibly have a lower test failure rate. The commentary considered that it is unknown what proportion of cases where there is a test failure would undergo a rebiopsy so another sample can be gained.

Table MSAC. 4 Concordance of the Oncomine™ Dx Target Test compared with the clinical utility standard (Oncomine™Focus Assay; NGS vs NGS)

		Clinical utility standard		
		Positive	Negative	Total
OdxT test	Positive	174	0	174
	Negative	1	166	167
	Total	175	166	341
		PPA = 174 / (174 + 1) = 99.4%	**NPA = 166 / (166 + 0) = 100%**	

Source: Table 2-15, p76 of the submission
NPA = negative percent agreement; OdxT = Oncomine Dx Target Test; PPA = positive percent agreement

Table MSAC. 5 Concordance of Oncomine™ Dx Target Test compared with Sanger Sequencing

		Sanger sequencing		
		Positive	Negative	Total
OdxT test	Positive	163	6	169
	Negative	1	164	165
	Total	164	170	334
		PPA = 163 / (163 + 1) = 99.4%	**NPA = 164 / (164 + 6) = 96.5%**	

Source: Table 1, p1 of Attachment 2.3 of the submission
NPA = negative percent agreement; OdxT = Oncomine Dx Target Test; PPA = positive percent agreement

Prognostic evidence

Evidence assessing whether *IDH1* variant status is a prognostic marker was provided in the submission, with heterogenous findings. Three studies were identified in the submission comparing either progression-free survival (PFS) or overall survival (OS) in subgroups of patients whose tumours had *IDH1* variants or were *IDH1* wildtype. The commentary identified another three studies reporting on the prognostic effect of *IDH1* variants in CCA. Insufficient detail was provided in the submission to know whether these three studies had been identified and excluded, or not

identified, as no inclusion criteria were provided in the submission, and no list of excluded studies was provided.

Two out of six studies reported that the median OS was significantly shorter in those with *IDH1* variants than in *IDH1* wildtype tumours (suggesting that *IDH1* variants correspond with having a poor prognosis). The remaining four studies reported no significant difference. The study in patients who most closely match the target population (Rimini et al. 2023) did report that those with *IDH1* variants had significantly worse survival on usual care (second-line chemotherapy or palliative care) than those with wildtype *IDH1* receiving usual care (HR 1.9, 95%CI 1.2, 3.0, p=0.0047). *IDH1* variant status may therefore be associated with poorer prognosis, but the evidence is too heterogeneous for any strong conclusion to be made.

Table MSAC. 6 Overview of prognostic studies reporting overall survival

Study	Patients	Subgroups	Median survival (95%CI)	Difference in median survival	HR (95% CI) p-value	Adjusted HR (95% CI) p-value
Goyal et al al. 2015	*104 patients with unresectable or metastatic (advanced disease) iCCA*	*IDH1v*	*15.0 months*	*-6.1 months*	*N/A p=0.17*	N/A
		IDH1wt	*20.1 months*			
Kinzler et al. 2023	*69 patients with iCCA (any stage)*	IDH1v	17.6 months (11.5 – 23.6)	*-0.9 months*	*N/A* p=0.69	N/A
		IDH1wt	18.5 months (13.7 – 23.4)			
Rimini et al. 2023	*119 patients with advanced iCCA who had progressed on first-line chemotherapy*	IDH1v	8.2 months	*-5.9 months*	**1.9 (1.2, 3.0) p=0.0047**	**1.7 (1.1, 2.7) 0.0256**
		IDH1wt	14.1 months			
Rimini et al. 2022	*284 patients with iCCA (any stage)*	*IDH1v*	N/A	*Tendency towards better OS in wt group*	*1.33 (0.93, 1.91) p=0.26*	N/A
		IDH1wt	N/A			
Ruzzenente et al. 2016 (n=36 with EH-PCC)	*36 patients with epCCA (any stage)*	*IDH1v*	*9.1 months*	*-20.5 months*	*N/A* ***p=0.043***	N/A
		IDH1wt	*29.6 months*			
Zhu et al. 2014	*154 patients with iCCA (any stage)*	*IDH1v*	*39.31 months*	*8.36 months*	*0.98 (0.58, 1.65) p=0.94*	N/A
		IDH1wt	*30.95 months*			

Source: Table 2-12 p69 of the submission

CI = confidence interval; epCCA = extrahepatic perihilar cholangiocarcinoma; HR = hazard ratio; iCCA = intrahepatic cholangiocarcinoma; *IDH1*v = isocitrate dehydrogenase 1 variant; *IDH1*wt = isocitrate dehydrogenase 1 wildtype; N/A = not available; OS = overall survival

The commentary noted that both arms of the key trial (ClarIDHy) were in patients with *IDH1* variants, meaning that any differences in health outcomes between treatment arms were not due to presence or absence of the biomarker.

Predictive evidence

The commentary noted that no predictive evidence was provided in the submission (i.e. no clinical evidence was provided showing a differential effect of ivosidenib in those with and without the biomarker). However, there is a biological rationale that ivosidenib is an IDH1 enzyme inhibitor.

Preclinical evidence in *ex vivo* samples (blast cells, bone marrow or peripheral blood samples) from humans with acute myeloid leukaemia with and without R132 variants in the *IDH1* gene showed that ivosidenib reduced the levels of intracellular 2-HG by 96-99.7% in samples with variants in *IDH1*, whereas 2-HG levels in wildtype samples were undetectable[8].

The commentary considered it is therefore reasonable to conclude that the presence of an *IDH1* variant would be predictive of a response to ivosidenib.

Change in management in practice

The commentary noted no change in management data were presented in the submission. However, given that an *IDH1* variant is required in order to be eligible for ivosidenib, it is reasonable to assume that the results of *IDH1* testing would result in a change in management. That is, that patients who are otherwise eligible for ivosidenib would receive it, if they have a variant that suggests they may benefit from the targeted treatment.

The sponsor estimated that redacted% of patients with histologically confirmed CCA would be tested for *IDH1* variants. It is unclear what this assumption is based on. A systematic review by Boscoe et al. 2019, found that the prevalence of *IDH1* variants in CCA is approximately 9.15%. The sponsor has assumed that redacted% of these cases are either diagnosed when the CCA is locally advanced or metastatic, or would progress to having advanced disease. They further assumed that all patients who have first-line systemic therapy for advanced or metastatic disease would progress while on first-line therapy, and require second-line treatment or palliation. The commentary noted it was unclear what proportion of patients would be well enough after progression on first-line therapy to tolerate second-line chemotherapy or ivosidenib. If it assumed that 9.15% of patients are *IDH1* variant positive at CCA diagnosis, 80% have locally advanced or metastatic disease or will progress to it, and that 100% of those who progress on first-line therapy receive ivosidenib, then 6.6% of those with CCA would potentially have a change in management due to the introduction of *IDH1* variant testing and ivosidenib.

Claim of codependence

The commentary considered the claim of codependence was not explicitly justified in the submission (i.e. no evidence was provided to demonstrate treatment effect variation in those with/without *IDH1* variants). However, there was a biological rationale for the way in which IDH1 p.R132X variants alter the behaviour of the *IDH1* gene, resulting in overexpression of IDH1 enzymes, which causes an excessive accumulation of the oncometabolite D-2-hydroxyglutarate (2-HG). Ivosidenib has been shown to bind to the altered IDH1 enzyme, reducing 2-HG levels (which interfere with cellular metabolism and epigenetic regulation, contributing to oncogenesis). There is therefore some logic for restricting the use of ivosidenib to those with *IDH1* variants.

13. Economic evaluation

The submission presented an economic evaluation comparing ivosidenib with palliative care/best supportive care (BSC) which was based on the ClarIDHy trial. The ClarIDHy trial was a randomised trial that compared ivosidenib to placebo in patients with locally advanced or metastatic CCA with IDH1 variants who had disease progression following at least one line of chemotherapy. The economic model also allowed for the inclusion of FOLFOX as a comparator in addition to BSC as a sensitivity analysis. Benefits were modelled from an unanchored matching-adjusted indirect comparison (MAIC) for PFS and from an anchored MAIC for OS, using data from the ClarIDHy trial (ivosidenib vs. placebo) and the ABC-06 trial (FOLFOX + active symptom control [ASC] vs. ASC

[8] Popovici-Muller Jet al. (2018) Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1 Mutant Cancers. *ACS Med Chem Lett*. 2018 Apr 12;9(4):300-5

alone). Although the inclusion of FOLFOX in the comparator arm was reasonable, the indirect treatment comparisons (ITCs) were based on trials with major transitivity issues.

The types of economic evaluation presented were a cost-utility analysis and a cost-effectiveness analysis. The outcomes were measured in terms of life-years (LYs) gained and quality-adjusted life-years (QALYs) gained. The economic evaluation was a partitioned survival analysis with three health states: progression-free (PF), progressed disease (PD) and death. Allocation to the health states was based on the survival curves for PFS and OS from the ClarIDHy trial. The commentary considered this reasonable. However, it noted the KM OS curve for the placebo arm was adjusted for treatment switching using the RPSFT method which is associated with inherent uncertainties. As such, the modelling of the OS curve for the placebo arm, and subsequently, the extrapolation of the OS, was also uncertain and considered that it must be interpreted with caution. Patients entered the model at the point of testing and in the PF health state. The submission presented the results of the economic evaluation for the population that is tested and then treated, using the codependent technology model. Therefore, the costs and benefits were 'diluted' by the large number of patients without *IDH1* variants within the model. The inclusion of IDH1 negative patients had no impact on the model, as the costs and health outcomes associated with these patients would cancel out in the proposed scenario, apart from the *IDH1* testing costs. The submission's economic model could be simplified to a trial (treated) population (as false positives and false positives were assumed to be zero in the model with no downstream effects), which does not include IDH1 negative patients, but takes into account the incremental testing costs between the current and proposed scenarios per trial/treated patient. The ICER from this simplified model was the same as that from the submission's codependent model.

The test parameters utilised in the economic evaluation were: 100% specificity and sensitivity with a *IDH1* variant prevalence of 9.15%. Therefore, for a proposed fee of $340 per test, the cost for identifying one patient with an *IDH1* variant was estimated to be $3,716.68[9]. The commentary considered this was an underestimate of the cost of testing and identifying one patient eligible for ivosidenib therapy as it did not consider: 1) patients who are diagnosed at an earlier stage of the disease and cured following surgical resection with no recurrence; 2) patients who have locally advanced or metastatic disease but are not suitable for active anticancer therapy and opt to receive palliative care. However, the commentary noted that varying this parameter had a minimal impact on the ICER. The probability of false positives and false negatives applied in the economic model was 0%. This was in line with MSAC Executive advice, and accordingly the analytical validity of the test was not investigated.

The submission's base case economic analysis was for the tested population and resulted in an ICER of $95,000<$115,000 /QALY (Table MSAC. 7). The results for the economic analysis in the trial population are presented in Table MSAC. 8.

[9] Cost of testing and identifying one patient = $340 ÷ 9.15%

Table MSAC. 7: Results of the stepped economic evaluation, in the testing population (discounted)

Step and component	Ivosidenib	SOC	Increment
Step 1: trial-based costs and outcomes (36 months)			
Costs	**redacted**	$24,309	**redacted**
LYs gained	0.725	0.682	0.043
Incremental cost/extra LY gained			**redacted**[1]
Step 2: extrapolated to 10 years			
Costs	**redacted**	$25,024	**redacted**
LYs gained	0.798	0.737	0.062
Incremental cost/extra LY gained			**redacted**[2]
Step 3: transformation into QALYs			
Costs	**redacted**	$25,024	**redacted**
QALYs	0.650	0.599	0.051
Incremental cost/extra QALY gained (base case)			**redacted**[1]

Note: the numbers may not be exact due to rounding in the "3.1_Ivosidenib cost-effectiveness model" Workbook provided in the submission.
Source: *Tabulated during the evaluation,* based on Table 3-23, p165 of the submission and the "3.1_Ivosidenib cost-effectiveness model" Workbook provided in the submission.
LYG = life years gained; SOC = standard of care; QALYs = quality adjusted life years
The redacted values correspond to the following ranges:
[1] *$95,000 to < $115,000*
[2] *$75,000 to < $95,000*

Table MSAC. 8: Results of the stepped economic evaluation, in the trial population (discounted)

Step and component	Ivosidenib	BSC	Increment
Step 1: trial-based costs and outcomes (36 months)			
Costs	**redacted**	$24,309	**redacted**
LYs gained	1.154	0.682	0.473
Incremental cost/extra LY gained			**redacted**[1]
Step 2: extrapolated to 10 years			
Costs	**redacted**	$25,024	**redacted**
LYs gained	1.413	0.737	0.676
Incremental cost/extra LY gained			**redacted**[2]
Step 3: transformation into QALYs			
Costs	**redacted**	$25,024	**redacted**
QALYs	1.159	0.599	0.560
Incremental cost/extra QALY gained (base case)			**redacted**[1]

Note: the numbers may not be exact due to rounding in the "3.1_Ivosidenib cost-effectiveness model" Workbook provided in the submission.
Source: Tabulated during the evaluation, based on the 'Setting and Results' and 'Model Tx (TP)' spreadsheets in the "3.1_Ivosidenib cost-effectiveness model" Workbook provided in the submission.
BSC = best supportive care; LYs = life-years; QALYs = quality-adjusted life years
The redacted values correspond to the following ranges:
[1] *$95,000 to < $115,000*
[2] *$75,000 to < $95,000*

14. Financial/budgetary impacts

The submission took an epidemiological approach to estimate the number of patients eligible for *IDH1* variant testing. The cost of *IDH1* variant testing to the MBS was estimated by assuming that this test would be performed in all patients with CCA, regardless of disease stage. The commentary noted this was consistent with the requested MBS item description for *IDH1* testing. The number of patients diagnosed with CCA in each year following the listing of *IDH1* testing was estimated on the basis of sponsor-commissioned incidence data from AIHW in 2015-2019, assuming a linear projection from 2019 to 2030 for each of iCCA, eCCA and biliary tract (not otherwise specified) CCA. The commentary noted this approach appeared reasonable.

The submission assumed a redacted% uptake rate of *IDH1* testing, based on clinician feedback which indicates that *IDH1* testing in CCA is currently being conducted through the Molecular Screening and Therapeutics (MoST) program for some patients and the clinical utility of testing is already well established in Australian clinical practice.

The cost associated with re-biopsy was not considered in the financial analysis. The commentary considered this appeared reasonable, as the likelihood of requiring a re-biopsy for the purpose of retrieving tumour tissue for *IDH1* testing is negligible given the proposal for testing at the point of diagnosis.

The financial analysis included MBS costs associated with electrocardiogram (ECG) monitoring in patients receiving ivosidenib treatment. As ivosidenib therapy is associated with an increased risk of prolongation of QTc interval, the ivosidenib product information recommends performing an ECG prior to treatment initiation, at least weekly during the first 3 weeks of therapy and at least monthly thereafter. Based on the average duration of treatment of 25.1 weeks as modelled in the economic evaluation, the submission assumed an average of 7.77 ECGs per patient treated with ivosidenib. The commentary noted this calculation was correct. However, it noted that the submission overestimated the number of patients likely to receive ivosidenib treatment, by assuming that 100% of patients with locally advanced or metastatic CCA would be treated with first-line systemic therapy and progress to receive second-line therapy and that redacted of these patients would receive ivosidenib, despite the aggressive advanced disease of the proposed target population. Some patients may not be suitable for active anticancer therapy and opt to receive palliative care instead. Thus, the commentary considered the MBS cost associated with ECG monitoring had been overestimated.

The base case financial analysis did not take into account the change in use of FOLFOX due to the listing of ivosidenib. Therefore, the MBS cost for intravenous infusion of chemotherapy (MBS item 13950; schedule fee: $118.30) was not included. Assuming that 45% of patients treated with ivosidenib would otherwise receive FOLFOX, the net MBS cost due to the proposed listing of *IDH1* testing and ivosidenib would reduce by 13%-15% from the submission's base case estimate as a result of a decrease in MBS services relating to chemotherapy administration.

In the submission, 80% benefit was assumed for both *IDH1* testing and EGC monitoring to estimate the net 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 MSAC.9 Estimated use and financial implications to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of *IDH1* testing						
Total CCA incidence	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Number of patients tested (uptake of redacted%)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Number of patients likely to receive a positive test result (9.15% positive rate)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Estimated financial implications of the *IDH1* testing to the MBS						
Cost to MBS less copayments (80% of the proposed MBS fee)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Cost to MBS less copayment (85% of the proposed MBS fee)[a]	*redacted[3]*	*redacted[3]*	*redacted[3]*	*redacted[3]*	*redacted[3]*	*redacted[3]*
Estimated financial implications for ECG monitoring to the MBS						
Cost to MBS less copayments (80% benefit, MBS item 11704)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Cost to MBS less copayment (85% of the proposed MBS fee)[a]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Net financial implications						
Net cost to MBS	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Net cost to MBS, assuming 85% benefit[a]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]

Source: Table 4-19 and Table 4-20, p181 of the submission.
CCA = cholangiocarcinoma; ECG = electrocardiogram; *IDH1* = isocitrate dehydrogenase 1
[a] *Additional analyses performed during the evaluation, by assuming 85% benefit as for out of hospital services.*

The redacted values correspond to the following ranges:
[1]< 500
[2]500 to < 5,000
[3]$0 to < $10 million

15. Other significant factors

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- CCA diagnosis can be often clinically challenging due to overlapping features with pancreatic cancers and carcinoma of unknown primary site. This may lead to 'diagnostic expansion' with testing being desired in patients whose primary tumour site is unclear, significantly increasing the population undertaking testing.
- Making the proposed testing pathologist-determinable is likely reasonable, to make best use of minimal biopsy samples.
- Whilst the current application proposed single gene testing of *IDH1* to determine eligibility for ivosidenib, in contemporary clinical practice genetic testing of CCA is performed using a gene panel.

Economic issues

- The modelling approach was reasonable overall, however, the base-case likely underestimated the ICER. All key drivers (extrapolation of survival for both arms, utilities, time horizon) favoured the intervention, making the robustness of the economic results uncertain. A revised base case may be more informative for MSAC and PBAC decision-making.
- The cost of testing did not take into account the potential increase in the population receiving *IDH1* testing if 'diagnostic expansion' occurs due to difficulty in clinically distinguishing CCA from carcinoma of unknown primary site, pancreatic carcinoma, and liver metastases of primary tumours located elsewhere.

Financial issues

- The submission overestimated the number of patients likely to be treated with ivosidenib, however the commentary's suggestions for revising the financial analysis were reasonable, and were accepted by the applicant in its pre-ESC response.
- If 'diagnostic expansion' occurs, then the service utilisation estimates and cost to the MBS would be higher than estimated.
- The proposed MBS fee ($340) aligns with *IDH1* testing in glioma (MBS item 73372), however there is broader inconsistency in the MBS fees of comparable items (e.g., $362.60 for *KRAS* in colorectal cancer (73338), and $397.35 for *EGFR* in lung cancer (73337)). A comparable gene panel test including fusions and sequencing has a fee of $1247 (MBS item 73437). If the fee for *IDH1* testing was increased, this would also increase the net financial cost to the MBS.

ESCs discussion

The ESCs noted that the integrated codependent application sought Medicare Benefits Schedule (MBS) listing *of isocitrate dehydrogenase 1 (IDH1)* testing for the evaluation of tier I IDH1 p.R132X variants to determine eligibility for ivosidenib on the Pharmaceutical Benefits Scheme (PBS) for treatment of patients with cholangiocarcinoma (CCA).

The ESCs noted CCA is adenocarcinoma of the bile ducts, and it is comprised of a variety of different tumours. The bile ducts are microscopic ducts in the liver that branch and join into bigger ducts to drain bile out of the liver. The duct is joined by the cystic duct out of the gall bladder merging with pancreatic duct in the pancreas to ultimately drain bile to the gastrointestinal tract into the duodenum. CCAs can occur in any of these sites from within the liver to where the bile duct drains through the pancreas into the duodenum. CCAs occurring in the liver arising from the microscopic bile ducts are classified as intrahepatic cholangiocarcinoma (iCCA), and those occurring in the perihilar (pCCA), or distal portions of the biliary tract (dCCA) are classified as extrahepatic cholangiocarcinoma (eCCA). The ESCs noted that CCAs can harbour a range of genetic alterations, some of which have actionable targets (although the relevant treatment may not be registered in Australia or funded). The majority of tumours that are potentially treatable with targeted therapies lie within the intrahepatic zone, that is, they are intrahepatic cholangiocarcinomas (iCCA). Up to 40% of iCCA will have potentially treatable targets identified by molecular testing and of these, the *IDH1* variants are most common. *IDH1* variants occur in ~20% of iCCAs. However *IDH1* variants are relatively rare in cholangiocarcinomas occurring outside the liver (0 to 3%). The ESCs noted while it could be argued to restrict testing to iCCA as the highest incidence of *IDH1* alterations occurs in the intrahepatic region, it considered that it was reasonable to include all CCA subtypes as they can be very difficult to distinguish in clinical practice.

The ESCs noted that in clinical practice in diagnostic pathology, CCA is considered a diagnosis of exclusion and a reasonable amount of clinical work-up (usually immunohistochemistry) is required

for cases of adenocarcinoma in the liver to exclude metastasis from elsewhere before suggesting a CCA diagnosis. The ESCs noted that carcinoma of unknown primary (CUP) site is often clinically challenging to diagnose as it commonly has a gene expression profile similar to that of CCA and may present in the liver. The ESCs considered it was highly likely that the proposed *IDH1* variant testing would be used in CUP cases to make an appropriate diagnosis. In addition, the ESCs noted the difficulty in distinguishing CCA of the distal common bile duct from the much more common pancreatic carcinoma. It is also common for pancreatic cancer to present with liver metastasis, and it is the metastasis that is biopsied and thought to be of 'pancreaticobiliary origin'. The ESCs considered that there would be a desire to use this MBS item to access testing when the primary tumour site was unclear, resulting in 'diagnostic expansion' which may potentially lead to significantly larger population and higher testing volumes than had been estimated. The ESCs considered that listing this testing could potentially result in more diagnostic tests, including repeat core biopsies. The ESCs anticipated that diagnostic expansion would also result in an apparent increased incidence of CCA in Australia, if incidence were estimated based on service volumes of this testing.

The ESCs noted and welcomed consultation input from two (2) consumer organisations and four (4) individuals, all of whom were specialists.

The ESCs noted the Pancare Foundation highlighted that patients with CCA have limited access to first line therapies, many of which come with adverse side effects leaving patients with a low quality of life. Thus, patients would benefit from a test to detect *IDH1* variants that would determine eligibility for ivosidenib. Patients living with rare and low-survival cancers such as cholangiocarcinoma, often experience high levels of financial toxicity and out-of-pocket costs including dietician and dietary supplements, physiotherapy services, psychological services, diagnostic testing and medication costs. Access to psychological support is also deemed beneficial for these patients. The ESCs noted specialist comment about the benefit of the test for *IDH1* that included gaining access to targeted therapy and improving the quality of life for these patients. It would enable them to spend more time with their families and less time will be spent as inpatients in hospitals. Public funding meant more people would have access to the test and the treatment. Another specialist pathologist from a genomics laboratory stated targeted treatments for CCA offers superior results and the molecular test would assist to readily identify the *IDH1* variants to help patients with a condition that has a very poor outlook. The feedback from Cholangiocarcinoma Foundation Australia stated that having access to ivosidenib could prolong disease-free time for patients and availability of the drug on the PBS would ensure it is more accessible while at the same time reducing financial burdens. The ESCs noted input from an oncologist with expertise in hepatobiliary cancers who stated that testing for *IDH1* is best performed as early as possible as it offers options in treatments. In addition, ivosidenib is the new standard of care internationally and the only drawback of *IDH1* testing is the cost and access limitations. The oncologist also stated that being able to access personalised therapy such as this would provide the patients with a sense of control, and testing should be done as an individual test or as part of a molecular panel.

The ESCs noted the clinical claim was that testing DNA from tumour tissue to detect an IDH1 p.R132X tier I variant, followed by targeted therapy with ivosidenib results in superior health outcomes compared to no testing and untargeted treatment/best supportive care in patients with locally advanced or metastatic CCAs. The ESCs noted that many common *IDH1* variants in CCA occur at codon R132 (e.g., p.R132C, R132L, R132G, R132H, R132S, and R132F), and so considered it was appropriate to test for *IDH1* alterations at this specific locus.

The ESCs considered it was reasonable for the proposed MBS item to be pathologist-determinable as often biopsies obtained from these tumours are very minimal and making it pathologist-determinable to triage the tissue would streamline the process. Noting the low cure rate from surgery in patients with CCA, the ESCs considered testing early on was less likely to lead to wastage of tissue, although also noted testing at diagnosis would encompass the approximately 10-15% of

patients who do not progress to advanced disease. On balance, the ESCs considered testing at diagnosis (as proposed) was likely preferable. The ESCs noted that testing can be performed on cytology samples (similar to samples as tested for lung cancer) although core biopsies may be more optimal for testing.

The ESCs noted that despite the proposed *IDH1* testing only referring to a genetic test, the proposed item descriptor defined the biomarker in terms of the corresponding protein variant, and considered the use of protein nomenclature risked creating the misconception that the testing was of protein rather than nucleic acid. The ESCs also noted the proposed item descriptor included "tier I", the standard nomenclature for classification of these somatic genetic variants. Whilst MSAC is committed to using internationally recognised genetics nomenclature, the ESCs considered that before the test is done, it will be known what genetic location (locus) is to be tested, but the classification of any variant detected would not be known. The ESCs therefore considered it would be more appropriate for the MBS item descriptor to describe the genetic biomarker to be tested without describing the result required for ivosidenib eligibility, i.e. "*IDH1* variant status". The ESCs considered the biomarker relevant to PBS treatment eligibility did not need to be included within the MBS item descriptor, and that it was acceptable for this to be defined under the PBS listing for ivosidenib.

The ESCs noted the proposed MBS fee for *IDH1* variant testing was $340, the same fee as the current MBS item 73372 for *IDH1/2* variant testing of tumour tissue from patients diagnosed with glioma or glioblastoma. The ESCs noted that other MBS listings of similar tests for *Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS)* testing in metastatic colorectal cancer (stage IV) (MBS item 73338, Fee $362.60) and *epidermal growth factor receptor* (*EGFR*) testing in non-small cell lung cancer (MBS item 73337, Fee $397.35) have higher fees than the proposed *IDH1* single gene testing. The ESCs questioned the inconsistency of currently listed MBS fees for similar tests, and noted that if the fee for *IDH1* variant testing was increased from the $340 aligning with other *IDH1* testing to instead align with the MBS fees for other comparable single gene tests then this would increase the cost of testing and reduce its cost-effectiveness.

The ESCs noted in real world practice, almost all laboratories in Australia undertake testing using gene panels for molecular characterisation of tumours (using the same panel for lung and colon cancers), and considered it was unlikely that a single gene test would be used in practice for CCA tumours. The ESCs noted that only undertaking single gene testing would potentially miss other alterations of emerging significance that are currently not funded e.g., *FGFR/NTRK* fusions. The ESCs considered that an MBS item for gene panel testing (including fusion testing) would futureproof testing for patients with CCA as more therapies emerge over time. Gene panel testing could potentially also detect alterations that are mutually exclusive with *IDH1* variants, such as *KRAS* other than p.G12C, which could potentially have 'value of knowing'. The ESCs noted that comparable (as it includes fusion testing) gene panel testing includes MBS item 73437 for non-small cell lung cancer (MBS fee of $1247).

ESC's proposed revisions to the proposed MBS item descriptor are below.

Table MSAC.10 ESC's proposed revisions to the proposed MBS item descriptor

Category 6 – PATHOLOGY SERVICES Group P7 – Genetics
XXXXX Detection in tumour tissue of *isocitrate dehydrogenase 1 (IDH1)* ~~p.R132X tier I~~ variant status, in a patient with histologically confirmed cholangiocarcinoma, to determine access to an isocitrate dehydrogenase 1 inhibitor under the Pharmaceutical Benefits Scheme (PBS). Applicable only once per lifetime
Fee: $340 Benefit: 75% = $255.00 85% = $289.00

ESC's deletions in strikethrough text.
Source: ESC

Overall, the ESCs considered the economic model structure was reasonable, and noted the base case incremental cost-effectiveness ratio (ICER) was $95,000 < $115,000 per quality-adjusted life year (QALY). The ESCs noted the economic analysis used a partitioned survival model with a time horizon of 10 years, which was substantially longer than median follow-up in key ClarIDHy trial (OS of 20.5-24.4 months) and the expected life expectancy of the patient cohort. The ESCs considered a time horizon of 7.5 years had been used in previous similar applications, although as the CCA patient cohort has more advanced disease a time horizon of 5 years would be more appropriate, which increased the ICER. The ESCs noted that the ICER was highly sensitive to the utility weights applied. The ESCs considered that the utility weights (derived from the ClarIDHy trial) appeared to be unusually high and clinically implausible for such a severe condition (with the value for the PFS state only just lower than the average health in recently reported Australian general population studies for this instrument), and considered that although the methodological approach to derive them had been appropriate, the resulting utility values lacked face validity.

In relation to the test, the ESCs agreed with the commentary that the cost of testing and identifying one patient eligible for ivosidenib had been underestimated. This stemmed from the assumption that all patients testing positive would proceed to treatment and did not take into account patients who undergo *IDH1* testing at an early stage of CCA and are subsequently cured, as well as those who may opt to receive palliative care for this aggressive condition. The ESCs noted that correcting this resulted in a small increase in the ICER (ranging between $95,000 < $115,000-) depending on how many patients were assumed to not receive ivosidenib in scenarios evaluated by the commentary.

Furthermore, the ESCs considered the impact on the ICER could be significant if a 'diagnostic expansion' occurred leading to a significantly larger population receiving this testing.

The ESCs noted that the key drivers of the model (extrapolation of survival for both arms, utility weights and time horizon) all favoured the intervention, which the ESCs considered reduced the robustness of the results, making a respecified economic base case potentially informative for MSAC and PBAC decision-making.

The ESCs noted that listing of *IDH1* testing for CCA patients was estimated to result in a net cost of $0 to < $10 million in Year 1 to $0 to < $10 million in Year 6 to the MBS. The ESCs noted that an epidemiological approach was utilised to estimate the number of patients who would receive treatment based on the CCA incidence data from the Australian Institute of Health and Welfare (AIHW) and historical growth rate. The ESCs agreed with the commentary that the Applicant Developed Assessment Report (ADAR) had overestimated the number of patients likely to be treated with ivosidenib. Consequently, the MBS costs for electrocardiograms (ECGs) to monitor patients receiving ivosidenib were likely to be lower than estimated. The ESCs noted the ADAR's overestimation was accepted by the applicant in its pre-ESC response.

The ESCs noted that sensitivity analyses indicated the financial results were largely stable under the scenarios tested. However, the ESCs also considered that potential increases in testing could

occur due to a “diagnostic expansion’. The ESCs considered that if the MBS fee for the proposed item were raised from aligning with other *IDH1* testing to instead aligned with other comparable MBS items, this would also increase the net financial cost to the MBS. Similarly, if the testing were implemented as a gene panel test to futureproof testing for patients with CCA, then this would likely be at a higher cost than $340 per test.

17. Applicant comments on MSAC’s Public Summary Document

The applicant had no comment.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website