

**7.07 IVOSIDENIB,  
Tablet 250 mg,  
Tibsovo<sup>®</sup>,  
Servier Laboratories Aust. Pty. Ltd.**

**1 Purpose**

- 1.1 The early re-entry resubmission sought the PBS listing of ivosidenib for the treatment of locally advanced or metastatic cholangiocarcinoma (CCA) in patients who have evidence of an *IDH1* variant and whose disease has progressed on at least one prior line of systemic therapy.
- 1.2 The resubmission was based on the PBAC decision to not recommend ivosidenib for this indication from its July 2024 meeting. This resubmission addressed some of the issues raised by the PBAC; see table below.

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Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed? Y/N
<b>Revision of the economic model</b>		
The PBAC considered that the time horizon in the base case (10 years), and the pre-PBAC response (7.5 years) was not justified given the patients in the proposed targeted population have advanced disease and a poor prognosis. The PBAC considered a 5-year time horizon would appropriately capture the benefits of ivosidenib (para 7.11)	The time horizon of the economic evaluation was updated to 5 years as per PBAC advice.	Y
The PBAC noted that there was uncertainty associated with the extrapolated benefit... the PBAC agreed with the ESCs that the extrapolations based on the exponential function were reasonable for both treatment arms (para 7.12)	OS extrapolation functions were revised to generalised gamma for ivosidenib, and Weibull for placebo.	N
The PBAC noted the utility weights used in the submission, derived from the HRQoL assessments in the ClarIDHy trial, were high (at or close to population norms) and appeared clinically implausible, especially in the PD health state... the PBAC considered that, given the lack of face validity and likely impact of limited trial QoL data, in this case the values used in the durvalumab submission (PF=0.857, PD=0.766) would be more reasonable. (para 7.13)	The Sponsor maintained that the utilities derived from the ClarIDHy clinical trial were most applicable to the economic evaluation of ivosidenib.	N
In the absence of any adjustment in outcomes, the PBAC considered it was reasonable for the ToT to be based on the trial data without being capped by the PFS curve. (para 7.14)	The sponsor maintained that it is reasonable to cap time on treatment at PFS.	N
<b>Price</b>		
The PBAC considered that ivosidenib would be acceptably cost-effective with an ICER no more than \$█████ <sup>1</sup> /QALY (para 7.16)	The resubmission proposed a █████% price reduction on the previously proposed effective price for ivosidenib. From \$█████ to \$█████ (AEMP)	Partially
<b>Financial estimates</b>		
The PBAC considered that 70% would be a more appropriate estimate of patients progressing to 2L ivosidenib treatment. The PBAC considered that this would also account for patients electing to receive ivosidenib so no additional adjustment for ivosidenib uptake is required. (para 7.17)	A rate of progression to 2L treatment was incorporated into the model, assumed to be 70%. The uptake rate of ivosidenib was increased to █████%.	Y
The PBAC agreed with DUSC that the <i>IDH1</i> test uptake should be increased from █████% to █████% as it is likely to become routine for clinicians to test all patients diagnosed with CCA. (para 7.17)	The uptake rate of the <i>IDH1</i> test was increased to █████%.	Y

AEMP = approved ex-manufacturer price; ESC = economic subcommittee; HRQoL = health related quality of life; ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression free survival; QALY = quality adjusted life year; QOL = quality of life; ToT = time on treatment.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

## 2 Background

2.1 Ivosidenib was included on the ARTG on 6th April 2023 for the following indication:

“For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (*IDH1*) R132 mutation after at least one prior line of systemic therapy.”

2.2 The PICO from the previous submission is presented below.

**Table 2: Key components of the clinical issue addressed by the July 2024 submission**

Component	Description
Population	<b>Test:</b> Adult patients with cholangiocarcinoma (CCA) <b>Treatment:</b> Patients with locally advanced or metastatic CCA who have disease progression following at least one line of chemotherapy and a confirmed isocitrate dehydrogenase 1 ( <i>IDH1</i> ) mutation
Intervention	<b>Test:</b> Tumour tissue testing for <i>IDH1</i> tier I variant status <b>Treatment:</b> Ivosidenib as second or third-line treatment for locally advanced or metastatic CCAs in those with <i>IDH1</i> p.R132X tier I variants
Comparator	<b>Test:</b> No testing <b>Treatment:</b> <ul style="list-style-type: none"> <li>• Primary comparator: palliative care</li> <li>• Secondary comparator: chemotherapy with 5-fluorouracil (5-FU) plus oxaliplatin (FOLFOX) or 5-FU plus irinotecan (FOLFIRI)</li> </ul>
Outcomes	<b>Test-related outcomes:</b> <b>Clinical utility of the test:</b> <ul style="list-style-type: none"> <li>• Treatment effect modification for ivosidenib based on <i>IDH1</i> p.R132X tier I variant status (predictive validity)</li> </ul> <b>Other test-related considerations:</b> <ul style="list-style-type: none"> <li>• Number estimated to be tested</li> <li>• Number needed to test (to identify one eligible case for ivosidenib)</li> <li>• Test turnaround time</li> <li>• Rate of re-biopsy (including test failure and inadequate sample rate)</li> <li>• Safety of re-biopsy</li> </ul> <b>Treatment-related outcomes:</b> <ul style="list-style-type: none"> <li>• Critical outcomes (GRADE): <ul style="list-style-type: none"> <li>○ Progression free survival</li> <li>○ Overall survival</li> <li>○ Objective response rate</li> </ul> </li> <li>• Important outcomes (GRADE) <ul style="list-style-type: none"> <li>○ Time from randomisation to discontinuation or death</li> <li>○ Health-related quality of life</li> </ul> </li> <li>• Safety and tolerability: <ul style="list-style-type: none"> <li>○ Treatment-emergent adverse events</li> <li>○ Physical examination and laboratory findings</li> </ul> </li> </ul>
Clinical claim	Testing deoxyribonucleic acid (DNA) from tumour tissue to detect <i>IDH1</i> p.R132X tier I variant, followed by targeted therapy with ivosidenib results in superior health outcomes compared to no testing and untargeted treatment/palliative care in patients with locally advanced or metastatic CCA.

Source: Table 1-2, p31 of the July 2024 submission

For more detail on PBAC’s view, see section 5 PBAC outcome.

### 3 Requested listing

3.1 As per the July 2024 submission, a standalone MBS item descriptor for testing *IDH1* variant status was proposed. The sponsor’s proposed item descriptor wording is shown in Table 3. The MSAC proposed revisions to the item descriptor as shown in Table 4. The proposed fee (100%) of \$340 aligns with the current MBS fees for testing *IDH1/2* variant status in for patients with confirmed glial neoplasm (73372 MBS item). Overall, MSAC considered *IDH1* genetic testing was comparatively safe, would have

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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. MSAC foreshadowed it would expeditiously reconsider this testing if the PBAC recommended ivosidenib (p5 1750 ratified Public Summary Document (PSD) – Aug 2024).

**Table 3: Proposed MBS item descriptor for IDH1 variant testing**

Category 6 – PATHOLOGY SERVICES
xxxxx Detection in tumour tissue of p.R132X tier 1 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

**Table 4: MSAC recommended MBS item descriptor for IDH1 variant testing**

Category 6 – Pathology Services Group P7 – Genetics
XXXXX Detection in tumour tissue of <i>isocitrate dehydrogenase 1 (IDH1)</i> 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

3.2 The resubmission accepted amendments to the PBS restriction as proposed by the Secretariat. The PBAC previously considered the appropriate restriction wording for specifying the target population would be: “The patient must have a test of tumour tissue confirming the presence of an *IDH1* R132 variant” (para 7.3, ivosidenib PSD, July 2024 PBAC meeting).

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Ivosidenib, oral tablet, 250 mg	1	60	2 (initial) 5 (continuing) 5 (grandfathering)	Published: \$25,058.29 Effective: \$ [redacted]	TIBSOVO Servier Laboratories (Aust.) Pty. Ltd.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
IVOSIDENIB					
Ivosidenib 250 mg tablet, 60	NEW	1	60	2	Tibsovo
<b>Restriction Summary [new 1] / Treatment of Concept: [new 1]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new/existing code]					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
<b>Episodicity:</b> [blank]					

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<b>Severity:</b> Locally advanced or metastatic
<b>Condition:</b> Cholangiocarcinoma
<b>Indication:</b> locally advanced or metastatic cholangiocarcinoma
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b>
The condition must be associated with a confirmed Isocitrate dehydrogenase 1 (IDH1) tier 1 variant The patient must have a test of tumour tissue confirming the presence of an IDH1 R132 variant
<b>AND</b>
<b>Clinical criteria:</b>
The patient must have had systemic therapy for this condition prior to initiating treatment with this drug for this condition.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have/have had a WHO performance status of 2 or less at treatment initiation with this drug
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this condition
<b>AND</b>
<b>Treatment criteria:</b>
Patient must be undergoing treatment with this drug class for the first time
<b>Caution:</b> Ivosidenib can cause dose-dependent prolongation of the heart rate-corrected QT (QTc) interval. At treatment initiation patients should undergo an electrocardiogram (ECG) to assess the heart rate-corrected QT (QTc) interval. Dose interruptions are recommended until QTc returns to ≤480 msec. Monitor ECGs at least weekly for two weeks following return of QTc. Permanently discontinue ivosidenib if QTc poses life threatening ventricular arrhythmia (Grade 4)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IVOSIDENIB					
Ivosidenib 250 mg tablet, 60	NEW	1	60	5	Tibsovo
<b>Restriction Summary [new 2] / Treatment of Concept: [new 2]</b>					
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new/existing code]				
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
	<b>Treatment Phase:</b> Continuing treatment				
	<b>Clinical criteria:</b>				
	Patient must have previously received PBS-subsidised treatment with this drug for this condition				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	The treatment must be the sole PBS-subsidised therapy for this condition				
	<b>AND</b>				
	<b>Clinical criteria:</b>				

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	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	<b>Caution:</b> Ivosidenib can cause dose-dependent prolongation of the heart rate-corrected QT (QTc) interval. At treatment initiation patients should undergo an electrocardiogram (ECG) to assess the heart rate-corrected QT (QTc) interval. Dose interruptions are recommended until QTc returns to $\leq 480$ msec. Monitor ECGs at least weekly for two weeks following return of QTc. Permanently discontinue ivosidenib if QTc poses life threatening ventricular arrhythmia (Grade 4)
<b>Restriction Summary [new 3] / Treatment of Concept: [new 3]</b>	
	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	<b>Clinical criteria:</b>
	<del>The condition must be associated with a confirmed Isocitrate dehydrogenase 1 (IDH1) tier I variant</del> <i>The patient must have a test of tumour tissue confirming the presence of an IDH1 R132 variant</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	The patient must have had systemic therapy for this condition prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have/have had a WHO performance status of 2 or less at treatment initiation with this drug
	<b>AND</b>
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [Date]
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	<b>Prescribing Instructions:</b> A patient may qualify for PBS-subsidised treatment under this restriction once only.
	<b>Prescribing Instructions:</b> For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	<b>Administrative Advice:</b> <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>
	<b>Caution:</b> Ivosidenib can cause dose-dependent prolongation of the heart rate-corrected QT (QTc) interval. At treatment initiation patients should undergo an electrocardiogram (ECG) to assess the heart rate-corrected QT (QTc) interval. Dose interruptions are recommended until QTc returns to $\leq 480$ msec. Monitor ECGs at least weekly for two weeks following return of QTc. Permanently discontinue ivosidenib if QTc poses life threatening ventricular arrhythmia (Grade 4)

Source: Table 1-4.1-5,1-6, of the resubmission  
IDH1 = isocitrate dehydrogenase 1

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## 4 Consideration of the evidence

### *Sponsor hearing*

4.1 There was no hearing for this item.

### *Consumer comments*

- 4.2 The PBAC noted and welcomed the input from individual (12), and organisational (5) contributors via the Consumer Comments facility on the PBS website. The PBAC also recalled consumer comments received in relation to the July 2024 consideration of ivosidenib. Comments indicated that current treatment options have limited efficacy and ivosidenib is considered effective in slowing disease progression and is less toxic than chemotherapy in the second line (2L) setting, but costs are prohibitive for patients without PBS subsidisation. Input also described the small number of PBS-subsidised treatment options for patients with CCA, which has a very poor prognosis, and the value of survival time in providing additional time with family.
- 4.3 The PBAC noted the advice received from Pancare Foundation, Liver Foundation and Cholangiocarcinoma Foundation Australia in support of the ivosidenib submission. Input from both Liver Foundation and Pancare noted that patients diagnosed with cholangiocarcinoma are often diagnosed late, have a poor survival prognosis and treatment results in serious physical side effects, major impact on quality of life and high financial burden. Comments noted the very limited alternative treatment options for CCA and that progression free survival (PFS) gain and the overall survival (OS) gain for patients treated with ivosidenib was considered meaningful to patients, given the limited survival rate for CCA. Comments from the two Cholangiocarcinoma Foundation Australia submissions noted personal experiences with CCA, including the physical, emotional and financial impact of the disease, side effects of current treatments and the need for equitable access to affordable and effective treatment options. The comments noted the value of a targeted treatment and the benefits of its oral administration.
- 4.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the ivosidenib submission as an “other supported application”. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ivosidenib, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, based on results of the ClarIDHy trial.

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<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

### Clinical claim

- 4.5 The PBAC recalled it previously considered that the clinical claim of superior comparative effectiveness for ivosidenib compared with BSC was reasonable, with a small PFS benefit and moderate OS benefit shown after adjustment for cross-over. However, the PBAC considered that the OS benefit was associated with uncertainty given the adjustment for cross-over and because the patient population in the ClarIDHy trial is likely to be fitter than the Australian population that is likely to be treated with ivosidenib. The PBAC recalled it previously considered that the clinical claim of superior comparative effectiveness for ivosidenib compared with FOLFOX is likely to be reasonable, however there is a high level of uncertainty due to the limitations of the ITC (paragraphs 6.48 and 6.50 ivosidenib PSD, July 2024 PBAC meeting).
- 4.6 The PBAC recalled it previously considered the clinical claim of inferior comparative safety for ivosidenib compared with BSC was reasonable and the clinical claim of superior comparative safety for ivosidenib compared with FOLFOX was uncertain as no formal safety comparison was possible, although FOLFOX is associated with substantial toxicity (paragraphs 6.49 and 6.51 ivosidenib PSD, July 2024 PBAC meeting).

### Economic analysis

- 4.7 To address the PBAC’s concerns regarding the cost-effectiveness of ivosidenib the resubmission presented an economic evaluation with revised inputs for the time horizon and overall survival extrapolation functions and a reduced price for ivosidenib (10% reduction, from \$1 to \$1 AEMP). The base case incremental cost-effectiveness ratio (ICER) in the resubmission was \$55,000 to < \$75,000 per quality-adjusted life year (QALY). The PBAC previously considered that ivosidenib would be cost-effective with an ICER of no more than \$75,000 to < \$95,000/QALY.
- 4.8 The resubmission did not fully revise the model as requested by the PBAC:
- The revised model did not apply the extrapolation functions the PBAC considered appropriate (exponential).
  - The model retained utility values derived from the ClarIDHy trial.
  - The model capped time on treatment at PFS without adjustment to the modelled outcomes.

**Table 5: Resubmission base case results**

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
IDH1 test + ivosidenib	\$1	\$1	1.009	0.528	\$1 <sup>1</sup> per QALY
No test + SOC	\$1		0.481		

Source: Table 3-25 ivosidenib resubmission

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

- 4.9 The resubmission reduced the time horizon from 7.5 to 5 years based on PBAC advice, but argued that truncating the analysis at 5 years is a conservative approach as it does not capture the expected longer-term benefits of treatment. The resubmission also argued that OS estimates from the ClarIDHy trial are likely to underestimate the survival observed in Australian clinical practice as the trial included 46.9% of patients who had received two previous lines of therapy, whereas patients are likely to receive ivosidenib as second line therapy in Australian clinical practice. The PBAC previously considered that the reduced time horizon was appropriate in the context of uncertain magnitude of clinical benefit (given the inherent uncertainty in the adjustment for cross-over and a potentially fitter population than expected in clinical practice) (para 7.11, ivosidenib PSD, July 2024 PBAC meeting).
- 4.10 The PBAC previously noted that there was uncertainty associated with the extrapolated benefit in the base case as the chosen functional forms appeared optimistic in terms of survival and were not clinically plausible. The PBAC considered that extrapolations for overall survival based on the exponential function were reasonable for both treatment arms (para 7.12, ivosidenib PSD, July 2024 PBAC meeting). In the resubmission the sponsor argued that the exponential function is a poor fit for the ivosidenib data, based on both statistical and visual fit, and consistently underestimates survival in the ivosidenib arm. The resubmission base case applied the generalised gamma function for extrapolation of the ivosidenib arm, and the Weibull function for extrapolation of the placebo arm. The resubmission stated that these functions were consistent with NICE considerations for ivosidenib and aligned with landmark analyses of patients alive at 6 and 2 months in the trial data (see Table 6 for ivosidenib and Table 7 for placebo ).

**Table 6: Landmark analysis of the proportion of patients alive at 6 and 12 months in the ivosidenib arm of ClarIDHy compared to the modelled evaluation (Generalised Gamma)**

Time	ClarIDHy (ivosidenib)	Modelled
6 months	68.8%	69.1%
12 months	42.9%	44.0%

Source: ClarIDHy CSR DCO2 Table 5; Attachment 3.1 – Ivosidenib cost-effectiveness model, 'Model\_Cx (TN, FN, SoC)'

- 4.11 Landmark analyses for the placebo arm included unadjusted values from ClarIDHy, values adjusted for cross-over, and OS from ABC-06, a study which compared FOLFOX with active symptom control in patients with 2L advanced biliary tract cancer (Lamarca et al., 2021).

**Table 7: Landmark analysis of proportion of patients alive at 6 and 12 months in the placebo arm of ClarIDHy compared to the modelled evaluation (Weibull) and ABC-06**

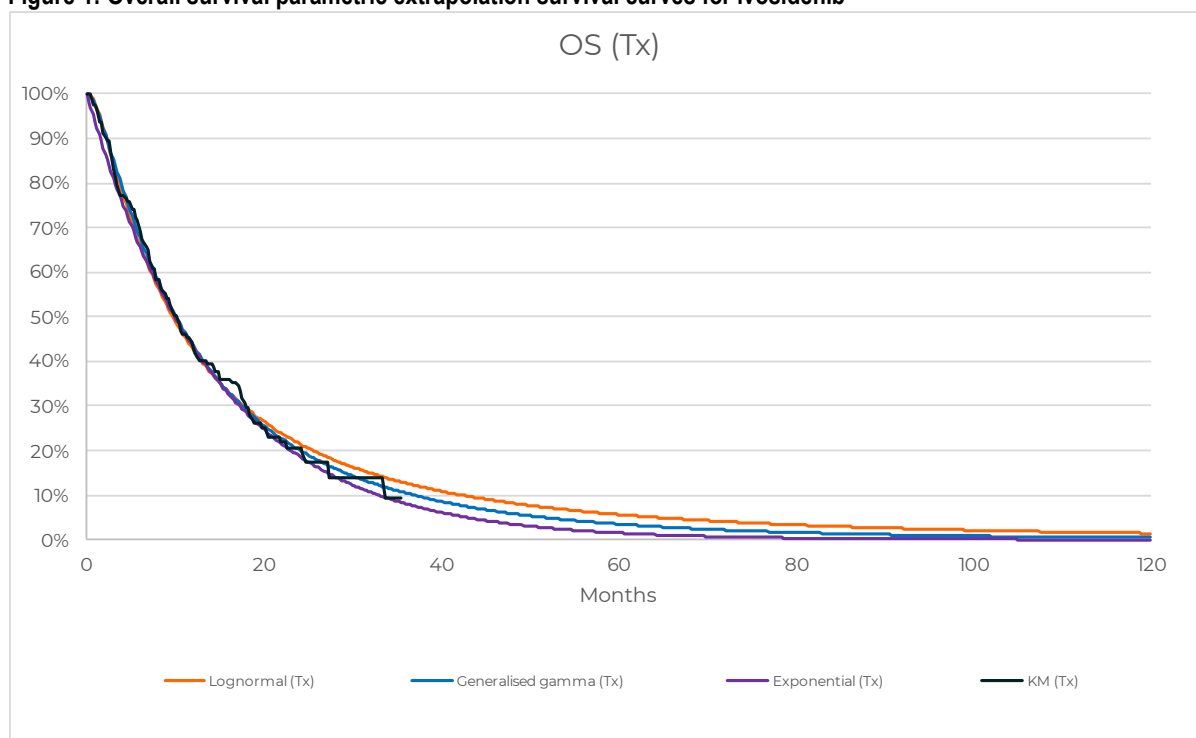
Time	ClarIDHy (unadjusted)	ClarIDHy (adjusted)	Modelled	ABC-06 (ASC)
6 months	57.4%%	47.5%	43.4%	35.5%
12 months	35.8%%	17.1%	18.1%	11.2%

Abbreviations: ASC, active symptom control; NE, not estimable

Source: ClarIDHy CSR DCO2 Table 5; Attachment 3.1 – Ivosidenib cost-effectiveness model, 'Model\_Cx (TN, FN, SoC)'; Lamarca et al. (2021)

4.12 As shown in Figure 1, the function applied to the ivosidenib arm in the resubmission revised model (generalised gamma) resulted in an incremental OS benefit that was more conservative than the function applied in the July 2024 submission (log normal), but more favourable than the function the PBAC considered appropriate (exponential).

Figure 1: Overall survival parametric extrapolation survival curves for ivosidenib

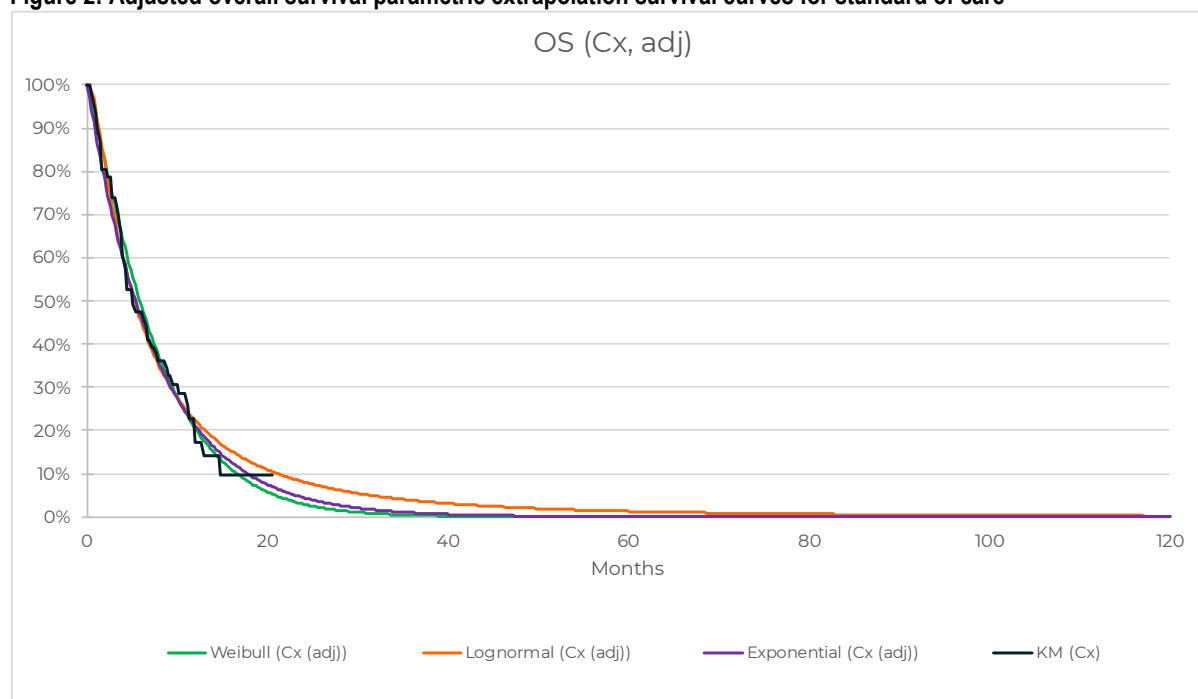


Source: Figure 3-4 ivosidenib resubmission

Abbreviations: Adj = adjusted; OS = overall survival; KM = Kaplan Meier; Tx = treatment

4.13 As shown in Figure 2 the function applied to the comparator arm in the resubmission revised model (Weibull) resulted in reduced OS compared to the July 2024 submission (log normal) and was therefore less conservative than the previous submission. It was also less conservative than the function the PBAC considered appropriate (exponential).

Figure 2: Adjusted overall survival parametric extrapolation survival curves for standard of care



Source: Figure 3-5 ivosidenib resubmission

Abbreviations: Adj = adjusted; OS = overall survival; Cx = comparator; KM = Kaplan Meier

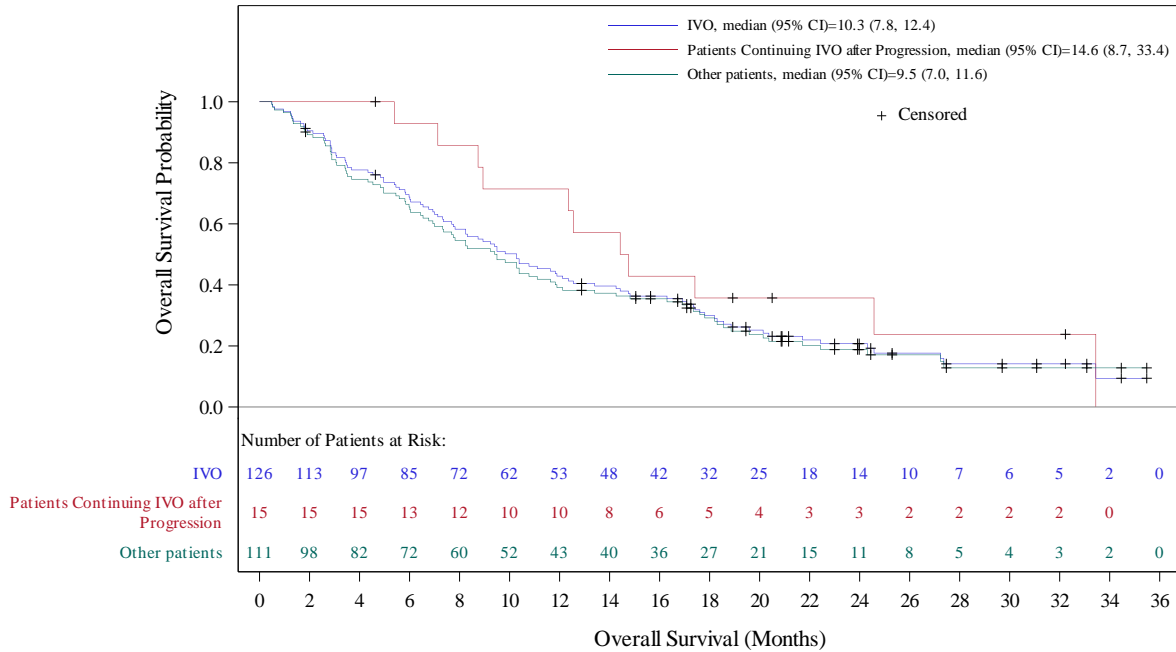
4.14 The PBAC noted the utility weights used in the July 2024 submission, derived from the HRQoL assessments in the ClarIDHy trial, were high (at or close to population norms) and appeared clinically implausible, especially in the PD health state. The PBAC considered that, given the lack of face validity and likely impact of limited trial QoL data, in this case the values used in the durvalumab submission (PF=0.857, PD=0.766) for biliary tract cancer would be more reasonable (para 7.13, ivosidenib PSD, July 2024 PBAC meeting). The resubmission noted that the March 2023 durvalumab submission used utility values from the TOPAZ-1 trial based on a Canadian value set (PF=0.857, PD=0.766). Although these values were accepted by the PBAC, the July 2023 durvalumab resubmission revised the utility values to reflect an Australian value set (PF=0.912, PD=0.807). The ivosidenib resubmission stated that utility values were not a main driver of the ICER and proposed that the values from the ClarIDHy trial should be retained in the base case (PF=0.852, PD=0.804). Application of the durvalumab utility values based on the Canadian value set increased the ICER by |%, however application of the durvalumab utility values based on the Australian value set reduced the ICER by |%.

4.15 The PBAC noted that in ClarIDHy patients were allowed to continue treatment with ivosidenib on disease progression, whereas this would not be allowed through the PBS based on the proposed restrictions. In the absence of any adjustment in outcomes, the PBAC considered it was reasonable for the time on treatment to be based on the trial data without being capped by the PFS curve (para 7.14, ivosidenib PSD, July 2024 PBAC meeting). The resubmission maintained that as the proposed restriction for

ivosidenib on the PBS would not allow use after progression, it is reasonable to cap time on treatment at PFS. The resubmission model did not make any adjustment to outcomes to account for the longer time on treatment in the trial. The resubmission modelled time on treatment was 5.8 months. When not limited to PFS, the modelled time on treatment increased to 6.7 months. The mean time on treatment in the ClarIDHy trial was 6.3 months, 5 (4%) patients remained on treatment at 24 months.

- 4.16 To consider the impact of treatment beyond progression in the ClarIDHy trial the resubmission provided OS KM curves for the subgroup of patients who received treatment beyond progression, the complement, and the ITT population (Figure 3). The resubmission noted that interpretation of the subgroup who received ivosidenib after progression is limited by the extremely small sample size, (n=15) and the inherent bias in this subgroup. The resubmission argued that patients who continued treatment beyond progression are likely to have more favourable prognostic factors, leading the treating clinician to believe they would continue to derive benefit from treatment. The resubmission argued that when comparing the OS estimate in those who did not continue to receive treatment beyond progression with the ITT population, the effect of treatment beyond progression is not significant. The resubmission also reported that clinicians have advised that, in addition to monitoring for signs of clinical deterioration, all patients with CCA are routinely scanned for progression every 2 to 3 months and treatment will be ceased when there is evidence of progression.
- 4.17 The resubmission also noted that capping time on treatment at PFS is consistent with the durvalumab July 2023 resubmission, where the base case model did not include costs for treatment beyond progression. As in the ClarIDHy trial, patients in the TOPAZ-1 trial were allowed to receive ongoing treatment at the discretion of the clinical investigator. Time on treatment was not capped at PFS in the March 2023 durvalumab submission model (but was updated in the pre-PBAC response) and the PBAC did not request the changed approach in the July 2023 resubmission (Table 5, durvalumab PSD, July 2023 PBAC Meeting).

Figure 3: Overall survival comparison in patients who continue treatment beyond progression



Source: Figure 3-10 ivosidenib resubmission

4.18 The resubmission provided univariate sensitivity analyses demonstrating the impact on the ICER of modifying the model inputs as requested by the PBAC (OS extrapolations for both arms based on exponential functions, utility values from the durvalumab submission, and ToT not capped at PFS). The resubmission also presented multivariate sensitivity analyses, including applying all values as requested by the PBAC as shown in Table 8. The resubmission noted that based on the PBAC’s preferred inputs the ICER increased to \$75,000 to < \$95,000/QALY, however the sponsor stated it is unable to reduce the price for ivosidenib further to achieve an ICER of \$55,000 to < \$75,000/QALY after incorporating these changes.

**Table 8: Sensitivity analyses**

Analyses	Incremental cost	Incremental QALY	ICER	% change from baseline
Base case (July 2024 submission)	\$█	0.560	\$█ <sup>1</sup>	–
Base case (resubmission)	\$█	0.528	\$█ <sup>2</sup>	
<b>Time horizon (base case: 5 years)</b>				
7.5 years	\$█	0.560	\$█ <sup>2</sup>	–%
<b>Utility weights (from ClarIDHy trial: PF=0.8524; PD=0.8043)</b>				
PF=0.857; PD=0.766 (Table 14, durvalumab PSD, March 2023 PBAC meeting)	\$█	0.518	\$█ <sup>2</sup>	█%
PF=0.912; PD=0.807 (Table 3, durvalumab PSD, July 2023 PBAC meeting)	\$█	0.549	\$█ <sup>2</sup>	–%
<b>Parametric model extrapolation for OS (Generalised gamma for ivosidenib, Weibull for placebo)</b>				
OS: exponential (both arms)	\$█	0.449	\$█ <sup>3</sup>	█%
<b>Costs</b>				
Using ToT curve (not limited by PFS) to model treatment cost for ivosidenib treatment	\$█	0.528	\$█ <sup>3</sup>	█%
Exclusion of terminal care costs	\$█	0.528	\$█ <sup>2</sup>	█%
<b>Other multivariate analyses</b>				
5 year time horizon, OS extrapolations exponential, duration of treatment based on trial ToT	\$█	0.449	\$█ <sup>3</sup>	█%
<b>PBAC specified parameters</b>				
5 year time horizon, durvalumab utilities (Mar 2023 submission), OS extrapolations exponential, duration of treatment based on trial ToT	\$█	0.443	\$█ <sup>3</sup>	█%

Values in italics were corrected for the submission overview.

The redacted values correspond to the following ranges:

<sup>1</sup> \$95,000 to < \$115,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$75,000 to < \$95,000

4.19 For the July 2024 submission, it was noted that the exclusion of terminal care costs had minimal impact on the result based on a time horizon of 10 years (Table 11, ivosidenib PSD, July 2024 PBAC meeting). Exclusion of terminal care costs for the resubmission model increased the ICER by █%.

4.20 Based on the PBAC’s July 2024 preferred inputs for time horizon, OS extrapolations and duration of treatment, but with utility values from ClarIDHy as proposed in the resubmission, the ICER increased to \$75,000 to < \$95,000/QALY.

### **Drug cost/patient/year**

4.21 The estimated drug cost/patient/course at the revised price (\$█ DPMQ) would be \$█, based on a course duration of 5.8 months, at a dose intensity of 95.9%. The estimated drug cost/patient/course in the July 2024 submission was \$█, based on the same course duration and dose intensity. The *IDH1* testing cost (to identify one patient eligible for ivosidenib treatment) would be \$█. This was unchanged in the resubmission.

### **Estimated PBS usage & financial implications**

4.22 Based on PBAC and DUSC advice the sponsor made the following changes to the financial estimates:

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- The uptake rate of the *IDH1* test was increased to |% (from |% in the previous submission).
- A rate of progression to 2L treatment was incorporated into the model, assumed to be 70% per DUSC feedback (assumed 100% in previous submission).
- The uptake rate of ivosidenib was increased to |% (previously |% to |%), as the rate of progression to 2L treatment already incorporates uptake.

4.23 The resubmission estimated a net cost to the PBS/RPBS of \$0 to < \$10 million in Year 6 of listing, with a total net cost to the PBS/RPBS of over the first 6 years of listing of \$10 million to < \$20 million; see table below. The submission estimated a net cost to MBS for *IDH1* testing of \$0 to < \$10 million in year 6 of listing, with a total net cost to MBS of \$0 to < \$10 million over the first 6 years of listing.

**Table 9: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients tested	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
Patients treated <sup>a</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>
Number of scripts dispensed <sup>b</sup>	<sup>2</sup>	<sup>2</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
<b>Estimated financial implications</b>						
Cost to PBS/RPBS	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>
Cost to MBS for testing	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>
Cost to MBS for increased ECG monitoring	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>
Net cost to PBS/RPBS/MBS	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>
<b>Previous submission (July 2024)</b>						
Number of patients tested	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
Patients treated	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
Number of scripts dispensed <sup>b</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
Cost to PBS/RPBS	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>
Net cost to MBS	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>
Net cost to PBS/RPBS/MBS	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>	\$  <sup>3</sup>

<sup>a</sup> Assumes 9.15% prevalence of *IDH1*m, 80% with advanced/metastatic disease and 70% progressing to second line treatment.

<sup>b</sup> Includes 14 scripts for 5 grandfathered patients in year 1. Assuming 5.62 scripts per incident patients treated with ivosidenib. The number of scripts was estimated based on a treatment duration of 25.11 weeks and a compliance rate of 95.9%. The number of scripts per grandfathered patients was estimated to be 2.81 (=5.62/2).

Source: Tables 4-21, 4-22 ivosidenib resubmission, Table 17 and 18 July 2024 ivosidenib submission

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> <500

<sup>3</sup> \$0 to < \$10 million

For more detail on PBAC's view, see section 7 PBAC outcome.

## 5 PBAC Outcome

- 5.1 The PBAC recommended ivosidenib, for treatment of locally advanced or metastatic cholangiocarcinoma with an *IDH1* mutation, in patients who have previously progressed on chemotherapy. The PBAC considered that there was a high clinical need for treatments for patients with locally advanced or metastatic cholangiocarcinoma, who have a very poor prognosis. The PBAC reiterated its previous advice that the clinical evidence indicated that ivosidenib had a small progression free survival and overall survival advantage compared with standard treatment, for the small subset of patients with IDH1 mutations. The PBAC noted that not all optimistic assumptions in the economic model had been revised as requested. The PBAC considered the incremental cost-effectiveness ratio (ICER) remained high at the proposed price in the resubmission when the PBAC preferred assumptions were included in the model, and a further price reduction would be required.
- 5.2 The PBAC considered that the proposed restriction criteria were appropriate but that a combined listing including initial, continuing and grandfather treatment would be preferred for simplicity.
- 5.3 The PBAC considered that the resubmission had addressed some of the outstanding issues identified at the July 2024 PBAC meeting via a respecified economic model and reduced price proposed in the resubmission. However, the PBAC noted that the resubmission had not applied all requested changes in the revised model. The revised model did not apply the OS extrapolation functions the PBAC considered appropriate (exponential), retained utility values derived from the ClarIDHy trial and continued to cap the time on treatment based on PFS without adjustment to the modelled outcomes.
- 5.4 The PBAC noted that the function applied to the ivosidenib arm in the resubmission revised model (generalised gamma) resulted in an incremental OS benefit that was more conservative than the function applied in the July 2024 submission (log normal), but more favourable than the function it previously considered appropriate (exponential). In addition, the function applied to the comparator arm in the resubmission revised model (Weibull) resulted in reduced OS compared to the July 2024 submission (log normal) and was therefore less conservative than the previous submission. The PBAC noted the arguments provided by the sponsor regarding the extrapolation functions for OS but maintained that there was uncertainty associated with the extrapolated benefit and that extrapolations for overall survival based on the exponential function were reasonable for both treatment arms (para 7.12, ivosidenib PSD, July 2024 PBAC meeting).
- 5.5 The PBAC noted that the model retained utility values derived from the ClarIDHy trial, which it previously considered appeared clinically implausible, especially in the PD health state. The PBAC previously considered that, given the lack of face validity and likely impact of limited trial QoL data, in this case the values used in the durvalumab submission (PF=0.857, PD=0.766, using the Canadian value set) for biliary tract cancer

would be more reasonable (para 7.13, ivosidenib PSD, July 2024 PBAC meeting). The PBAC noted that application of the durvalumab utility values based on the Canadian value set increased the ICER by 1% to \$55,000 to < \$75,000/QALY, however application of the durvalumab utility values based on the Australian value set (PF=0.912, PD=0.807) reduced the ICER by 1% to \$55,000 to < \$75,000/QALY. The PBAC noted that the ICER was not sensitive to the source of utilities and considered that use of the utility values from the ClarIDHy trial, as proposed in the resubmission, was reasonable.

- 5.6 The PBAC noted that in ClarIDHy patients were allowed to continue treatment with ivosidenib on disease progression, whereas this would not be allowed through the PBS based on the proposed restrictions. The Committee maintained that in the absence of any adjustment in outcomes, it was reasonable for the time on treatment to be based on the trial data without being capped by the PFS curve (para 7.14, ivosidenib PSD, July 2024 PBAC meeting).
- 5.7 The PBAC noted that the base case ICER in the resubmission was \$55,000 to < \$75,000 per QALY and recalled it previously considered that ivosidenib would be cost-effective with an ICER of no more than \$55,000 to < \$75,000/QALY. Based on the PBAC's preferred inputs (as per paragraphs 5.4-5.6) the ICER increased to \$75,000 to < \$95,000/QALY. The PBAC considered that ivosidenib would be considered cost-effective at the price required to achieve an ICER of \$55,000 to < \$75,000/QALY with these inputs. This consideration was in the context of a small progression free survival and moderate overall survival advantage compared with standard treatment, for the small subset of patients with *IDH1* mutations (para 7.1, ivosidenib PSD, July 2024 PBAC meeting), with a high level of uncertainty in the magnitude of clinical benefit due to the inherent uncertainty in the adjustment for cross-over, a potentially fitter population than expected in clinical practice (para 7.11 ivosidenib PSD, July 2024 PBAC meeting) and exclusion of FOLFOX as the comparator (para 7.9 ivosidenib PSD, July 2024 PBAC meeting).
- 5.8 The PBAC considered that the changes to financial estimates applied in the resubmission were appropriate and consistent with DUSC advice on the July 2024 submission.
- 5.9 The PBAC recommended that ivosidenib should not be treated as interchangeable on an individual patient basis with any other drugs.
- 5.10 The PBAC advised that ivosidenib is not suitable for prescribing by nurse practitioners.
- 5.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for ivosidenib:
  - a) The treatment is not expected to provide a substantial improvement in efficacy over best supportive care, although it is expected to provide a small but clinically relevant improvement;

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- b) The treatment is expected to address a high clinical need, however other treatments for CCA are available in earlier lines;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.12 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

**Outcome:**

Recommended

## 6 Recommended listing

6.1 Add new item:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
Ivosidenib, oral tablet, 250 mg	1	60	2 (initial) 5 (continuing) 5 (grandfathering)	TIBSOVO Servier Laboratories (Aust.) Pty. Ltd.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
IVOSIDENIB					
Ivosidenib 250 mg tablet, 60	NEW	1	60	5	Tibsovo

Restriction Summary [new 1] / Treatment of Concept: [new 1]	
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new/existing code]
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Episodicity:</b> [blank]
	<b>Severity:</b> Locally advanced or metastatic
	<b>Condition:</b> Cholangiocarcinoma
	<b>Indication:</b> locally advanced or metastatic cholangiocarcinoma
	<b>Clinical criteria:</b>
	The patient must have a test of tumour tissue confirming the presence of an IDH1 R132 variant
	<b>AND</b>
	<b>Clinical criteria:</b>
	The patient must have had systemic therapy for this condition prior to initiating treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have/have had a WHO performance status of 2 or less at treatment initiation with this drug
	<b>AND</b>

	<b>Clinical criteria:</b>
	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	<b>Prescriber instructions:</b> Confirm that evidence of the presence of a pathogenic variant of the <i>IDH1</i> gene is documented/retained in the patient's medical records once only with the first PBS prescription.
	<b>Caution:</b> Ivosidenib can cause dose-dependent prolongation of the heart rate-corrected QT (QTc) interval. At treatment initiation patients should undergo an electrocardiogram (ECG) to assess the heart rate-corrected QT (QTc) interval. Dose interruptions are recommended until QTc returns to $\leq 480$ msec. Monitor ECGs at least weekly for two weeks following return of QTc. Permanently discontinue ivosidenib if QTc poses life threatening ventricular arrhythmia (Grade 4)

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **7 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **8 Sponsor's Comment**

Servier welcomes the positive recommendation made by the PBAC. Servier wishes to thank the cholangiocarcinoma clinical and patient communities for providing valuable input to inform the PBAC's recommendation. Servier looks forward to working with the Department of Health and Aged Care to help facilitate access to ivosidenib on the PBS at the earliest available opportunity.