7.08 DURVALUMAB, Solution concentrate for I.V. infusion 120 mg in 2.4 mL vial, Solution concentrate for I.V. infusion 500 mg in 10 mL vial, Imfinzi®, AstraZeneca Pty Ltd.

1 Purpose

1.1 The early re-entry resubmission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the first-line treatment of patients with advanced biliary tract cancer (BTC).

1.2 The resubmission was based on the PBAC decision to not recommend durvalumab for this indication at the March 2023 meeting. This resubmission addressed the issues raised by PBAC; see table below and further discussion under 'Consideration of the evidence'.

Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed?
Restriction criteria		
• The PBAC considered the listing incorporating the ESC and Secretariat's proposed changes (description of patient population) was appropriate and agreed with DUSC that patients with ampullary cancer should be excluded (paragraph 7.3, March 2023 PBAC Public Summary Document (PSD)).	• Revised restriction was as proposed by ESC and the Secretariat, and also excluded patients with ampullary cancer.	Yes.
Revision of inputs to the economic evaluation		
• The PBAC noted the economic model was sensitive to the time horizon with a change from 10 years to 5 years increasing the ICER to $[redacted][1]/ QALY (from $[redacted][2]/ QALY). The PBAC considered a time horizon of 10 years for this condition was not justified and a time horizon of 5 years would be more appropriate (paragraph 7.7, March 2023 PBAC PSD). • The PBAC suggested provision of an economic model with a reduced time horizon as above and a revised price that results in an ICER of less than $75,000/ QALY (paragraph 7.9, March 2023 PBAC PSD). • The pre-PBAC response to the March 2023 model had altered the model so that use of durvalumab beyond progression was removed. That approach was maintained in the resubmission.	• A time horizon of 7.5 years was applied along with a price reduction to EMP $[redacted] per 500 mg vial (compared to $[redacted] in the previous submission and $[redacted] in the pre-PBAC response). • The resubmission also used an Australian value set for calculation of utility values and changed the distribution of use, with increased public hospital use. • ICER $[redacted][3]/ QALY	A longer time horizon than that considered appropriate by the PBAC was applied. The changes to utilities and distribution of use were not requested by the PBAC.
Revision of inputs to the financial estimates		
• The PBAC noted the pre-PBAC response provided revised financial estimates which (i) assumed 22% of patients with liver cancer have IHCC (ii) updated patient co-payments (iii) included the cost for [redacted][4] grandfathered patients (as a proxy for accounting for the estimated [redacted][4] grandfathered patients receiving less treatment to account for treatment already received) (iv) reduced vial price for durvalumab and (v) assumed no treatment beyond progression. The PBAC considered the utilisation of durvalumab in the pre-PBAC response was likely to be overestimated with optimistic assumptions regarding uptake ([redacted]% each year), proportion of patients with PS 0 – 1 ([redacted]%) and proportion of patients with liver cancer assumed to have IHCC (22%). The PBAC noted the sensitivity analyses conducted by DUSC for each of these assumptions resulted in a substantial reduction in the overall costs (paragraph 7.8, March 2023 PBAC PSD). • The PBAC suggested provision of revised financial estimates incorporating a revised price and addressing the issues outlined (paragraph 7.9, March 2023 PBAC PSD).	The resubmission applied a revised price, as used in the economic model, and stated that the assumptions used for uptake ([redacted]%), proportion assumed to have IHCC (22%) and proportion with PS 0 - 1 ([redacted]%) would remain.	Discussed, but except for a revised price, no other changes were made.

Source: 6.05 durvalumab PSD, March 2023 PBAC meeting.

EMP = ex-manufacturer price; IHCC = intrahepatic cholangiocarcinoma; PS = performance status

The redacted values correspond to the following ranges:

[1] $135,000 to < $155,000

[2] $115,000 to < $135,000

[3] $55,000 to < $75,000[4] < 500

2 Background

Registration status

2.1 Durvalumab was TGA registered on 4 April 2023 for use in combination with gemcitabine and cisplatin for the treatment of patients with locally advanced or metastatic biliary tract cancer.

Previous consideration

2.2 A submission for durvalumab, in combination with gemcitabine and cisplatin (GemCis), was considered by the PBAC at its March 2023 meeting and was not recommended (Table 1).

2.3 The PBAC considered the outstanding issues could be resolved in a simple resubmission for durvalumab using the early re-entry pathway, and the following changes may address the outstanding issues (paragraph 7.9, durvalumab Public Summary Document (PSD), March 2023 PBAC meeting):

- Provide revised restriction criteria as outlined in Table 1.
- Provide an economic model with a reduced time horizon (5 years) and a revised price that results in an ICER of less than $75,000 per QALY.
- Provide revised financial estimates incorporating a revised price and addressing the issues outlined in Table 1.

2.4 The key components of the clinical issues addressed in the resubmission are presented below.

Table 2: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Patients with advanced BTC (i.e. patients with previously untreated, unresectable locally advanced, or metastatic disease, and patients with recurrent disease after curative surgery or after completion of adjuvant therapy).
Intervention	Durvalumab 1,500 mg in combination with GemCis every 3 weeks up to 8 cycles[a] followed by durvalumab 1,500 mg every 4 weeks until disease progression.
Comparator	Placebo in combination with GemCis every 3 weeks up to 8 cycles followed by placebo every 4 weeks until disease progression.
Outcomes	OS, PFS, ORR, DoR, HRQoL and safety.
Clinical claim	Durvalumab in combination with GemCis is superior in terms of efficacy and non-inferior in terms of safety overall when compared to placebo in combination with GemCis.

Source: Table 1.1, p10 of the resubmission.

BTC = biliary tract cancer; DoR = duration of response; GemCis = gemcitabine plus cisplatin; HRQoL = health related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression free survival.

[a] Durvalumab was administered once per cycle with GemCis on day 1, and GemCis administered again on day 8 of each 3-week cycle.

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

3 Requested listing

3.1 The March 2023 PBAC PSD (paragraph 3.1) detailed suggested wording changes from the Secretariat to the description of the patient population in the requested

restriction. These changes were adopted in the resubmission, along with further text describing BTC.

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
DURVALUMAB 500 mg / 10 mL solution for infusion 120 mg / 2.4 mL solution for infusion	Published price $12,012.07 (public hospital) $12,220.65 (private hospital) Effective price $[redacted] (public hospital) $[redacted] (private hospital)	1,500 mg	7 (initial treatment) 5 (continuing treatment)

Source: Table 1.2, p11 of the resubmission.

Category / Program:	Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Severity:	Locally advanced, metastatic, or recurrent
Condition:	Biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer)
PBS Indication:	Locally advanced, metastatic, or recurrent biliary tract cancer
Treatment phase:	Initial treatment
Restriction:	☒Authority Required (Streamlined)
Administrative Advice:	No increase in the maximum amount or number of units may be authorised.
Administrative Advice:	No increase in the maximum number of repeats may be authorised.
Administrative Advice:	Special Pricing Arrangements apply.
Patient Population	Patient must be initiating treatment and have either of the following: (i) locally advanced biliary tract cancer that is untreated with systemic anti-cancer therapy in the unresectable setting, (ii) metastatic biliary tract cancer that is untreated with systemic anti-cancer therapy in the metastatic setting **OR** Patient must be transitioning from existing non-PBS to PBS subsidised supply of this drug and have either of the following at the time this drug was initiated: (i) locally advanced biliary tract cancer that is untreated with systemic anti-cancer therapy in the unresectable setting, (ii) metastatic biliary tract cancer that is untreated with systemic anti-cancer therapy in the metastatic setting
Clinical criteria:	Patient must have/have had a WHO performance status score of no greater than 1 at treatment initiation with this drug **AND** The treatment must be/have been initiated with both: (i) gemcitabine, (ii) cisplatin **AND** The treatment must be prescribed with up to a certain number of repeat prescriptions dependent on either of which: (i) up to 7 repeats for initial treatment to complete 8 cycles, (ii) remainder repeats to complete 8 cycles for patients transitioning from non-PBS to PBS-subsidised supply provided the disease has not progressed
Treatment phase:	Continuing treatment
Severity:	Locally advanced, metastatic, or recurrent
Condition:	Biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer)
PBS Indication:	Biliary tract cancer
Restriction:	☒Authority Required (Streamlined)
Administrative Advice:	No increase in the maximum amount or number of units may be authorised.
Administrative Advice:	No increase in the maximum number of repeats may be authorised.
Administrative Advice:	Special Pricing Arrangements apply.
Clinical criteria:	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition

	AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have developed disease progression while being treated with this drug for this condition

3.2 The resubmission requested an effective ex-manufacturer price of $[redacted] per 500 mg in 10 mL vial. This is [redacted]% lower than the price proposed in the March 2023 submission.

3.3 The PBAC PSD stated (paragraph 3.8) that DUSC had noted that patients with ampullary carcinoma were excluded from the pivotal trial (TOPAZ-1), and DUSC considered that the restriction should specify the exclusion of this patient population due to the potential uncertainty in its management in practice (treatment with either small bowel, pancreatic or biliary regimens). Paragraph 7.3 of the PBAC PSD noted that the PBAC agreed with DUSC that patients with ampullary cancer should be excluded. The resubmission appears to have addressed this issue by including 'intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder cancer' in the description of the condition in the proposed criteria.

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 the Medical Oncology Group of Australia (MOGA) via the Consumer Comments facility on the PBS website.

4.3 The MOGA expressed its strong support for the durvalumab resubmission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the TOPAZ-1 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for durvalumab, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with GemCis.

Comparative effectiveness

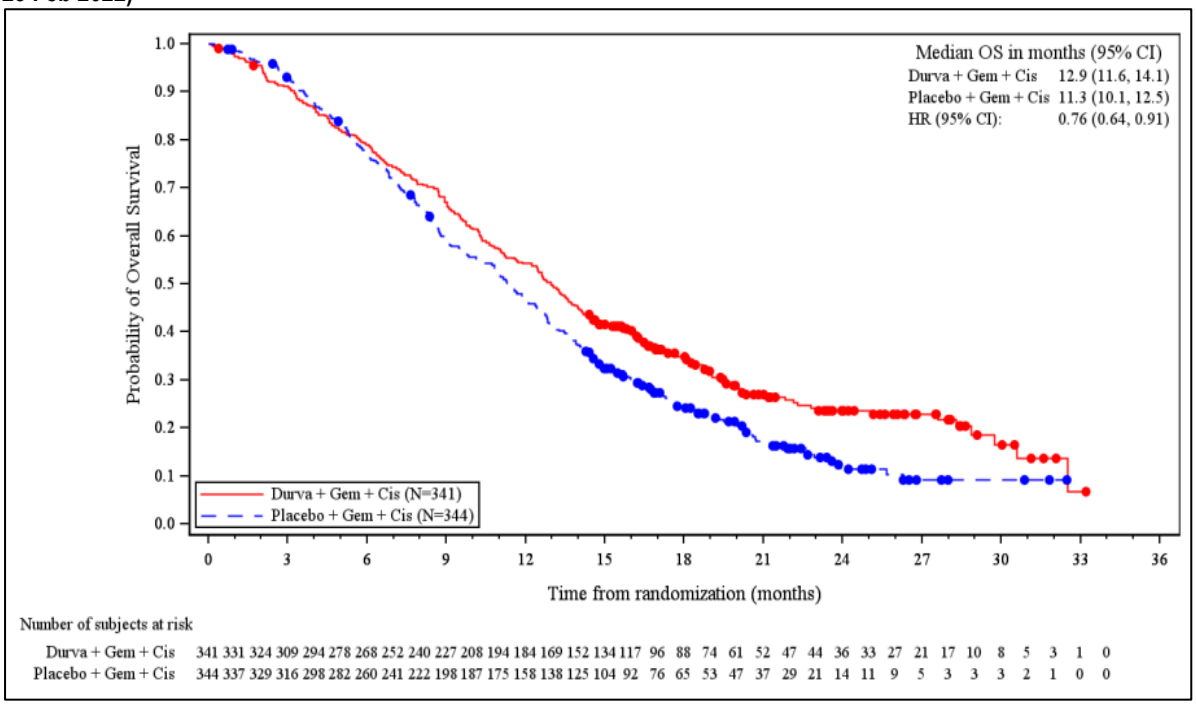
4.4 No additional clinical evidence was provided in the resubmission.

4.5 The March 2023 consideration of durvalumab for first-line treatment of advanced BTC was based on one randomised, double-blind trial comparing durvalumab + GemCis to placebo + GemCis, TOPAZ-1 (N=685).

[1] Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol* 2017; 28(10):2340-2366.

4.6 The PBAC noted a modest improvement in overall survival (OS) for patients treated with durvalumab + GemCis compared to placebo + GemCis (HR 0.76; median incremental gain of 1.6 months, 23.6% alive vs 11.5% alive at 24 months; see Figure 1). The PBAC noted a small improvement in progression free survival (PFS), with a HR of 0.76, median incremental gain of 1.5 months, and 16.0% not progressed vs 6.6% not progressed at 12 months. Overall, the PBAC considered the claim that durvalumab + GemCis is superior in terms of effectiveness to placebo + GemCis was reasonable (paragraph 7.5, durvalumab PSD, March 2023 PBAC meeting) with durvalumab in combination with chemotherapy providing a moderate added benefit in PFS and OS (paragraph 7.1, durvalumab PSD, March 2023 PBAC meeting).

Figure 1: Kaplan-Meier plot of overall survival, TOPAZ-1 FAS, additional 6.5-month follow-up (data cut-off 25 Feb 2022)



Source: Figure 2.1, p18 of the resubmission.
CI = confidence interval, Cis = cisplatin; CSR = clinical study report; Durva = durvalumab; FAS = full analyses set; Gem = gemcitabine; HR = hazard ratio; OS = overall survival.
FAS was defined as all randomised patients and analysed on an intention-to-treat basis
Hazard ratio and 95% confidence interval are nominal only.

4.7 The March 2023 submission claimed durvalumab + GemCis did not add substantial toxicity when compared to placebo + GemCis in the treatment of advanced BTC, and the PBAC considered the clinical claim regarding safety was reasonable (paragraphs 6.25 and 6.27, durvalumab PSD, March 2023 PBAC meeting). The PBAC noted durvalumab + GemCis was associated with more immune-related adverse events (AEs) compared to placebo + GemCis but considered overall the toxicity of durvalumab + GemCis was manageable (paragraph 7.6, durvalumab PSD, March 2023 PBAC meeting).

Economic evaluation

4.8 The PBAC advised that the resubmission should provide an economic model with a reduced time horizon (5 years) and a revised price that results in an ICER of less than $75,000 per QALY. The resubmission provided an economic model with a time horizon of 7.5 years, use of a different value set to calculate utility values, altered public/private hospital proportions and a reduced price to arrive at an ICER of $55,000 to < $75,000 / QALY. As an early re-entry resubmission, the revised economic analysis has not been independently evaluated.

4.9 The specific changes made to the model were as follows:

- Time horizon of 7.5 years: The resubmission stated that since a proportion of patients treated with durvalumab + GemCis will experience long-term survival, and available guidance states that lifetime horizons are appropriate in instances where different interventions have an impact on cost and outcomes over a patient's lifetime (ISPOR 2012; NICE 2013; Briggs 2006), the PBAC's suggested time horizon of 5 years was too short. The resubmission also cited the July 2020 PBAC consideration that a 7.5-year time horizon was reasonable to assess the cost-effectiveness of atezolizumab in combination with bevacizumab for the treatment of hepatocellular carcinoma (HCC) (paragraph 7.9, atezolizumab plus bevacizumab PSD, July 2020) and the July 2008 consideration of sorafenib, where the PBAC accepted a 10-year time horizon. The resubmission added that the PBAC's acceptance of a 5-year time horizon for regorafenib for the second-line treatment of unresectable HCC (regorafenib PSD, March 2018) supported a longer time horizon (i.e. 7.5 years) for durvalumab given the earlier treatment setting. Finally, the resubmission cited PBAC statements for nivolumab (paragraph 7.10, nivolumab PSD, November 2021) and pembrolizumab (paragraph 7.10, pembrolizumab PSD, November 2021), covering treatment of oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and HER2-negative carcinoma of the gastro-oesophageal junction. The resubmission provided the following text from both PSDs: "…it had previously recommended a 5-year time horizon in the second-line treatment setting for a similar patient population and considered a 7.5-year time horizon may be reasonable, given the earlier treatment setting…". This statement did not fully reflect the PBAC's considerations, as for example the pembrolizumab PSD stated "The PBAC considered a 7.5-year time horizon was optimistic and a 5-year time horizon would be preferable given the median duration of follow up in KN590 was 9.8 months and 12.6 months in the chemotherapy and pembrolizumab arms, respectively, and the poor prognosis of the patient population. However, the PBAC noted it had previously recommended a 5-year time horizon in the second-line treatment setting for a similar patient population and considered a 7.5-year time horizon may be reasonable, given the earlier treatment setting, if other model assumptions were conservative".

- Use of an Australian value set (Norman 2023) to calculate utility values: This was not a change specified by the PBAC. The March 2023 PBAC PSD stated (paragraph 6.39) that the ESC had noted an Australian value set was now available and ESC considered it would be informative to see the impact on the ICER of using this value set. Table 3 provides the utility values used in the resubmission model along with those used in the March 2023 model.
- Revised EMP of $ per 500 mg vial: The price used in the March 2023 submission was $ per 500 mg vial and in the March 2023 pre-PBAC response was $.
- Distribution of use in the public/ private hospital setting: the resubmission stated this was updated to reflect the distribution of services for atezolizumab for the treatment of HCC in calendar year 2021, based on Services Australia data. The public/private split was altered from 41.6%/ 58.4% in the March 2023 submission to 42.2%/ 57.8%. Increased public hospital use decreases the cost of durvalumab per administration.

Table 3: Utility values used in the updated economic model and the March 2023 model

	Progression free survival	Progressive disease
Australian value set (Norman 2023) - resubmission	0.912	0.807
Canadian value set - March 2023 submission	0.857	0.766

Source: Table 2.5, p23 of the resubmission.

4.10 Table 4 provides the results of the updated economic evaluation, and the results of the March 2023 economic evaluation are included for reference.

Table 4: Results of the updated economic evaluation and results of the March 2023 economic evaluation

Steps and resources	Durvalumab + GemCis	Placebo + GemCis	Increment
Step 1: TOPAZ-1 (time horizon 19 months; costs of interventions and IV infusion costs) - updated			
Costs	$	$5,210	$
LYs	1.009	0.941	0.068
Incremental cost per life year gained (updated)			$[1]
Step 1: TOPAZ-1 (time horizon 19 months; costs of interventions and IV infusion costs) - March 2023			
Costs	$	$5,216	$
LYs	1.009	0.941	0.068
Incremental cost per life year gained (March 2023)			$[2]
Step 2: Step 1 + clinical trial extrapolated to 7.5 years - updated			
Costs	$	$5,210	$
LYs	1.524	1.163	0.360
Incremental cost per life year gained (updated)			$[3]
Step 2: Step 1 + clinical trial extrapolated to 10 years - March 2023			
Costs	$	$5,216	$
LYs	1.568	1.174	0.394
Incremental cost per life year gained (March 2023)			$[4]
Step 3: clinical trial extrapolated to 7.5 years including all resource use[a] - updated			
Costs	$	$66,793	$
LYs	1.524	1.163	0.360
Incremental cost per life year gained (updated)			$[3]
Step 3: clinical trial extrapolated to 10 years including all resource use[a] - March 2023			
Costs	$	$66,995	$
LYs	1.568	0.947	0.394
Incremental cost per life year gained (March 2023)			$[4]
Step 4: trial extrapolated to 7.5 years; all resource use and transformed QALYs - updated			
Costs	$	$66,793	$
QALYs	1.297	0.994	**0.303**
Incremental cost per QALY gained (base case - updated)			**$**[3]
Step 4: trial extrapolated to 10 years; all resource use and transformed QALYs - March 2023			
Costs	$	$66,995	$
QALYs	1.259	0.947	**0.312**
Incremental cost per QALY gained (base case March 2023)			**$**[5]

Source: Table 2.9, p27-28 of the resubmission; Table 12 of the March 2023 PBAC PSD.
GemCis = gemcitabine + cisplatin; IV = intravenous; QALY = quality adjusted life years
[a]Includes costs for disease management, subsequent anti-cancer treatments, management of AEs, and terminal care costs.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$455,000 to < $555,000*
[3] *$55,000 to < $75,000*
[4] *$75,000 to < $95,000*
[5] *$115,000 to < $135,000*

4.11 The following table provides the results for the base case and 5-year time horizon using the March 2023 model, and steps through the changes made to generate the resubmission model.

Table 5: Change in model results with parameter and input changes used by the resubmission

	Incremental costs ($)	Incremental QALYs	ICER ($/QALY)
March 2023 consideration			
Base case (10 year time horizon)	[redacted]	0.312	[redacted][1]
7.5-year time horizon		0.286	[redacted][1]
5-year time horizon		0.238	[redacted][2]
Impact on model results – from model with 5-year time horizon with resubmission changes applied			
Treat to progression[a]	[redacted]	0.238	[redacted][1]
Price reduction (to $[redacted] per 500 mg vial)		0.238	[redacted][3]
7.5-year time horizon		0.286	[redacted][3]
Change in utilities (based on Australian value set)		0.303	[redacted][3]
Change in public/ private hospital split (to 42.2%/ 57.8%)		0.303	[redacted][4]

Source: Table 14 of the March 2023 PBAC PSD; Excel workbook 'Attachment 1 – Imfinzi durvalumab BTC CEA Updated Early Re-entry July 2023'.

[a] The pre-PBAC response to the March 2023 model had altered the model so that use beyond progression was removed. That approach was maintained in the resubmission.

The redacted values correspond to the following ranges:

[1] $115,000 to < $135,000

[2] $135,000 to < $155,000

[3] $75,000 to < $95,000

[4] $55,000 to < $75,000

4.12 The economic model, with a 5-year time horizon, assuming no treatment beyond progression and applying drug prices, utilities, and all other inputs as per the March 2023 model[2] resulted in an ICER of $115,000 to < $135,000 per QALY. Table 5 shows the impact of each change to the model made by the resubmission, as follows:

- The reduction in durvalumab price to $[redacted] per 500 mg vial decreased the ICER by 32%, to $75,000 to < $95,000 per QALY. A durvalumab price of $[redacted] per 500 mg vial (a further 17% reduction) would be required to achieve an ICER of less than $75,000 per QALY.
- Extending the time horizon to 7.5 years, instead of the 5 years requested by the PBAC, brought the ICER to $75,000 to < $95,000 per QALY, a further decrease of 13%.
- Changing the utility values to those based on an Australian value set decreased the ICER by a further 5%, to $75,000 to < $95,000 per QALY.

[2] The durvalumab price was $[redacted] per vial; utility values were based on a Canadian value set (0.857 for progression-free and 0.766 for progressed disease); the split in public/private hospital use was 41.6% public and 58.4% private.

- Changing the public/private hospital split had minimal impact, with a further 0.02% decrease, but brought the ICER to less than $75,000 at $55,000 to < $75,000 per QALY.

4.13 The changes not specified by the PBAC (utility values and public/private hospital split) had a small impact on the ICER, but nonetheless contributed to the ICER reaching a value less than $75,000.

4.14 The resubmission provided a sensitivity analysis applying utility values based on the Canadian value set, which were used in the March 2023 economic model. Those results are in Table 6, along with results using the time horizon recommended by the PBAC (5 years), and an analysis using a 5-year time horizon and utility values as per the March 2023 submission.

Table 6: Results of sensitivity analyses – utility values and time horizon

	Incremental costs ($)	Incremental QALYs	ICER ($/QALY)	Change (%) to base case ICER
Base case	[redacted]	0.303	$[redacted][1]	-
Health state utilities (base case: TOPAZ-1 Australian value set; PFS 0.912 and PD 0.807)				
Canadian value set (PFS 0.857 and PD 0.766) (#1)	[redacted]	0.286	[redacted][2]	6%
Time horizon (base case: 7.5 years)				
5 years (#2)	[redacted]	0.252	[redacted][2]	14%
Multi-variate analysis (health state utilities and time horizon)				
#1 and #2	[redacted]	0.238	[redacted][2]	21%

Source: Table 2.9, p27 of the resubmission; Excel workbook 'Attachment 1 – Imfinzi durvalumab BTC CEA Updated Early Re-entry July 2023'.

PFS = progression free survival; PD = progressive disease

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$75,000 to < $95,000*

4.15 As presented by the resubmission, alteration of utility values, to those used in the March 2023 submission based on a Canadian value set, increased the ICER/ QALY to $75,000 to < $95,000.

4.16 Applying a 5-year time horizon (as previously considered appropriate by the PBAC, see paragraph 2.4) resulted in an ICER of $75,000 to < $95,000/ QALY. When utility values as applied in the March 2023 submission (based on a Canadian value set) and a 5-year time horizon were used, the ICER increased to $75,000 to < $95,000/ QALY.

4.17 The pre-PBAC response argued that a time horizon of 7.5 years was appropriate on the basis of previous PBAC submissions, specifically the 10-year time horizon for sorafenib for advanced HCC in patients with unresectable disease, the 7.5 year horizon for atezolizumab + bevacizumab for unresectable locally advanced or metastatic BCLC stage B or stage C HCC who have not received prior systemic treatment, the 5-year horizon for regorafenib for unresectable HCC in a later line setting and the 7.5 year horizon for nivolumab and pembrolizumab for upper GI cancers.

Drug cost/patient/year

Table 7: Updated effective drug cost[a] per patient for proposed and comparator drugs

	Durvalumab + GemCis		Placebo + GemCis	
	Model	**Financial estimates (Durvalumab only[b])**	**Model**	**Financial estimates**
Mean duration (months)	7.87	8.24[c]	4.55	Not included
Cost/patient/month	$[redacted][d]	$[redacted][e]	$806[d]	
Cost/patient/course	Durvalumab + GemCis: $[redacted] Durvalumab: $[redacted]	$[redacted]	$3,669	
Cost/patient/month previous submission	$[redacted]	$[redacted]	$806	
Cost/patient/course previous submission	Durvalumab + GemCis: $[redacted] Durvalumab: $[redacted]	$[redacted]	$3,675	

Source: Excel workbook 'Attachment 1 – Imfinzi durvalumab BTC CEA Updated Early Re-entry July 2023'; Attachment 2 Imfinzi durvalumab BTC BIM Updated Early Re-entry_July 2023'; Table 15, durvalumab PBAC PSD, March 2023.

GemCis = gemcitabine + cisplatin

[a] Effective EMP of durvalumab $[redacted]; costs of durvalumab and GemCis per administration were estimated as a weighted average of the public and private hospital dispensed effective price for maximum amounts (DPMAs) (public hospital: 42.2%; private hospital: 57.8%). The weighted average cost per administration was $[redacted] for durvalumab and $271.84 for GemCis. Durvalumab treatment was delivered every 3 weeks when in combination with GemCis and every 4 weeks in monotherapy.

[b] The financial estimates did not consider the use of GemCis in its calculations.

[c] Calculation applied based on duration of treatment of 35.7 weeks (35.7 × 12/52 = 8.24 months).

[d] Calculation applied: cost per patient per course / mean duration.

[e] Calculation applied based on total cost to PBS/RPBS in Year 1: $20 million to < $30 million/ 500 to < 5,000 patients / 8.24 months = $[redacted]

4.18 The cost per patient per month and per course for durvalumab + GemCis has decreased in the resubmission, largely due to the reduction in durvalumab price, along with the slightly shorter treatment duration given treatment was ceased at progression.

Estimated PBS usage & financial implications

4.19 The PBAC previously considered the utilisation of durvalumab in the March 2023 pre-PBAC response was likely to be overestimated, with optimistic assumptions regarding uptake ([redacted]% each year), proportion of patients with PS 0 – 1 ([redacted]%) and proportion of patients with liver cancer assumed to have IHCC (22%). The PBAC noted the sensitivity analyses conducted by DUSC for each of these assumptions resulted in a substantial reduction in the overall costs (paragraph 7.8, durvalumab PSD, March 2023 PBAC meeting). The PBAC requested a resubmission provide revised financial estimates incorporating a revised price and addressing these issues.

4.20 The resubmission stated that after consideration of the sensitivity analyses conducted by DUSC, the sponsor will maintain the initial assumptions. The resubmission added that the sponsor was confident the financial estimates were quite certain and accurate, given the performance of the early access program (EAP). The EAP had < 500 patients enrolled in the first 6 months, March 2022 to August 2022 and a total of 500 to < 5,000 patients enrolled from March 2022 to April 2023.

4.21 In regard to the proportion of patients with PS 0 – 1 ([redacted]%), the resubmission stated this assumption was maintained as it was based on the best available evidence from a literature review (Brungs 2017) and was also validated by advisory board oncologists. In consideration of the March 2023 submission, DUSC had commented that the proposed patient population is often old and frail and noted that Brungs 2017 had only included patients who received chemotherapy and did not include patients receiving best supportive care (Table 16, durvalumab PSD, March 2023 PBAC meeting).

4.22 In regard to the uptake rate of [redacted]%, the resubmission stated this assumption was maintained based on the performance of the EAP (described in paragraph 4.20). The pre-PBAC response noted that other immunotherapies, such as atezolizumab for HCC which is another example of a treatment with a high unmet clinical need and no new treatment options in a long time, saw a substantial uptake (5,000 to < 10,000 scripts) in the first year on the PBS.

4.23 In regard to the proportion of patients with IHCC, the resubmission did not include further discussion. The March 2023 submission had assumed 15% of patients with liver cancer have IHCC and this proportion was increased to 22% in the Pre-Sub-Committee Response (PSCR) and remained at 22% in the resubmission.

4.24 The pre-PBAC response for the March 2023 submission had reduced the number of grandfathered patients to < 500 from the original < 500, to account for differences in treatment duration for grandfathered patients within the early access program. That number of grandfathered patients (in Year 1) was maintained in the resubmission. The pre-PBAC response for the March 2023 submission had also updated the duration of treatment to reflect no treatment beyond progression, resulting in a duration of treatment of 35.7 weeks, with 6.7 scripts for initial treatment and 3.9 scripts for continuing treatment. These inputs were maintained for the resubmission.

4.25 The only change made by the resubmission to the estimated financial implications was the reduced vial price of $[redacted] EMP per 500 mg vial, compared to $[redacted] used in the March 2023 submission and $[redacted] used in the March 2023 pre-PBAC response. Patient and script numbers remain the same as those presented in the March 2023 pre-PBAC response. The revised financial estimates are presented in Table 8.

Table 8: Estimated use and revised financial implications[a]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients initiating	[redacted][b1]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients initiating - previous submission	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients initiating – pre-PBAC response	[redacted][b1]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Scripts dispensed[c]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Scripts dispensed[d] - previous submission	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Scripts dispensed[c] - pre-PBAC response	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net financial implications						
Cost to PBS/RPBS (less copayments) ($)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Cost to MBS ($)	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4
Total cost to Government						
Net cost to Government ($)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]5	[redacted]5
Net cost to Government - previous submission ($)	[redacted]5	[redacted]5	[redacted]5	[redacted]6	[redacted]6	[redacted]6
Net cost to Government - pre-PBAC response ($)	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]6

Source: Table 4.8, p35; Table 4.21, p42 of the resubmission.

[a] The financial estimates did not consider the use of GemCis in its calculations; all estimates are for durvalumab use only.

[b] Includes < 500 grandfathered patients.

[c] Assumed 10.59 scripts per patient.

[d] Assumed 11.7 scripts per patient.

The redacted values correspond to the following ranges:

[1] 500 to <5,000

[2] 10,000 to <20,000

[3] $20 million to < $30 million

[4] $0 to < $10 million

[5] $30 million to < $40 million

[6] $40 million to < $50 million

4.26 The revised estimated net cost to Government was $20 million to < $30 million in Year 1, and a total of $100 million to < $200 million over the first 6 years of listing. This compared to estimated costs of $200 million to < $300 million over the first 6 years of listing based on the March 2023 submission, and $200 million to < $300 million based on the pre-PBAC response.

4.27 As the resubmission did not alter utilisation estimates as requested, sensitivity analyses have been conducted replicating the changes used by DUSC in March 2023 (Table 9).

Table 9: Sensitivity analyses - revised financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Base case ($)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][5]
Number of patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	-
Uptake (base case: [redacted]% each year) ($)							
Yr 1: [redacted]%; Yr 2: [redacted]%; Yr 3: [redacted]%; Yr 4: [redacted]%; Yr 5 – 6: [redacted]%	[redacted]	[redacted]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted](-17%) [5]
Number of patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	-
Proportion with WHO PS 0-1 (base case: [redacted]%)							
[redacted]% ($)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted](-22%)[5]
Number of patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	-
Proportion with liver cancer that have IHCC (base case: 22%) ($)							
15%	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted] (-14%)[5]
Number of patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	-
Uptake, PS 0 – 1 and proportion with IHCC (base case: [redacted]%, [redacted]%, [redacted]%, respectively) ($)							
Uptake [redacted]% in Yr 1 to [redacted]% in Yr 6; PS 0-1 of [redacted]%; IHCC 15%	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][1]	[redacted][1]	[redacted] (-44%) [4]
Number of patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	-

Source: Table 4.21, p42 of the resubmission; Excel workbook 'Attachment 2 Imfinzi durvalumab BTC BIM Updated Early Re-entry, July 2023'.

IHCC = intrahepatic cholangiocarcinoma; PS = performance status; WHO = World Health Organization; Yr = year

The redacted values correspond to the following ranges:

[1] $20 million to < $30 million

[2] $30 million to < $40 million

[3] $10 million to < $20 million

[4] $90 million to < $100 million

[5] $100 million to < $200 million

[6] 500 to < 5,000

4.28 The changes in utilisation originally assessed by DUSC had considerable impact on the financial estimates. Decreasing uptake reduced the estimated net cost over 6 years by 17% to $100 million to < $200 million. Decreasing the proportion of patients with WHO PS 0-1 reduced the estimated net cost over 6 years by 22% to $100 million to < $200 million. Reducing the proportion of patients with IHCC decreased estimated net cost over 6 years by 14% to $100 million to < $200 million. When all three of these changes were combined, estimated net cost to Government was substantially reduced, to $90 million to < $100 million over the first 6 years of listing, a 44% decrease.

4.29 The pre-PBAC response reiterated that the sponsor is confident that the financial estimates provided in the resubmission are certain and accurate given the performance of the EAP which is based on the TOPAZ-1 enrolment criteria (over

500 to < 5,000 patients were stated to have enrolled since March 2022), and the global performance of durvalumab.

Financial management – Risk Sharing Arrangements

4.30 The resubmission stated that the sponsor is willing to discuss the terms of a risk share arrangement (RSA) for the listing of durvalumab + GemCis for the treatment of BTC with the PBAC and the Department. No further detail was provided.

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

5 PBAC Outcome

5.1 The PBAC recommended the listing of durvalumab for the treatment of advanced biliary tract cancer. The PBAC considered that durvalumab in combination with chemotherapy provides a moderate improvement in overall survival and a small improvement in progression free survival compared to chemotherapy alone. The PBAC considered that the amendments made in the resubmission, including changes to the economic model and a reduced price had sufficiently addressed the Committee's previous concerns.

5.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of durvalumab would be acceptable at the price proposed in the submission.

5.3 The PBAC recalled the comments received from individuals, health care professionals and organisations for the March 2023 submission, and noted the Medical Oncology Group of Australia's strong support for the current submission. The PBAC considered there is a moderate to high clinical need for more effective treatments in this patient population who generally have a poor prognosis.

5.4 The PBAC noted that subsequent to consideration of the March 2023 submission, pembrolizumab has also been shown to be effective in biliary tract cancer[3], and the NCCN v2.2023, ESMO 2023 and UpToDate June 2023 guidelines included stronger endorsement for the use of durvalumab.

5.5 The PBAC noted that the revised restriction had appropriately addressed its previous advice with the exclusion of patients with ampullary carcinoma by describing the condition as 'intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder cancer'. The PBAC advised the initial and continuing criteria could be combined into a single restriction (with 5 repeats) covering both treatment phases. The PBAC considered the clinical criteria requiring treatment to be initiated in

[3] Kelley RK, Ueno M, Changhoon Y et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2023; 401: 1853 – 1865.

combination with GemCis was adequate to ensure appropriate clinical use of durvalumab.

5.6 The PBAC recalled it had previously accepted the clinical claims of superior efficacy and manageable safety versus gemcitabine and cisplatin (GemCis) alone were reasonable.

5.7 The PBAC considered the results of the economic analysis to have moderate certainty, noting some uncertainty with the efficacy estimates due to the short duration of follow-up (22-23 months) and most of the survival gain being in the progressive disease state, although also noted the availability of the results for the pembrolizumab trial in the same indication (KEYNOTE-966) provided additional confidence in the efficacy estimates. The PBAC further noted there was some uncertainty with the modelled benefits due to the potentially optimistic time horizon which required extrapolation of the clinical data.

5.8 The PBAC noted with the reduced price for durvalumab that the ICER was $75,000 to < $95,000/QALY, however this relied on changes not specified by the PBAC, specifically revised utility values based on the Australian value set, revised public/private hospital split and a modelled time horizon of 7.5 years. The PBAC noted revision of the utility values only had a small impact on the ICER and considered use of the Australian value set to be appropriate. The PBAC considered the 7.5-year time horizon to be reasonable in the context of models previously considered and accepted, the moderate certainty for the efficacy estimates and the extent of the extrapolation of the clinical data, and on the basis that there was only a moderate increase in the ICER to $75,000 to < $95,000/QALY with the use of a 5-year time horizon. Thus the PBAC advised that the revised economic analysis and price proposed in the resubmission addressed previous concerns regarding the cost-effectiveness of durvalumab.

5.9 The PBAC noted the resubmission revised the financial estimates to apply the reduced effective price, however did not revise the uptake rates, proportion of patients with a performance status of 0 - 1 or the proportion of patients assumed to have IHCC. The resubmission and pre-PBAC response maintained that the assumptions used in the March 2023 submission were appropriate and considered the estimates to be certain and accurate given the performance of the early access program (over 500 to < 5,000 patients were stated to have enrolled since March 2022), and the global performance of durvalumab. However, the PBAC remained concerned that the financial estimates were overestimated and considered that the sensitivity analyses based on the DUSC proposed inputs (Table 9) with estimated net cost to Government of $90 million to < $100 million (as per paragraph 4.28) provide a more plausible estimate of the likely financial impact.

5.10 The PBAC considered that although there was a low risk of use outside the restriction, an RSA with expenditure caps may be appropriate to manage use in patients with a

performance status of 2 or more for whom the cost effectiveness of durvalumab was uncertain.

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 durvalumab:

a) The PBAC considered treatment is expected to provide a moderate improvement in efficacy, over chemotherapy alone, and on this basis the criteria of proving a substantial and clinically relevant improvement in efficacy was not met.

b) The treatment is not expected to address a high and urgent unmet clinical need due to the availability of alternative therapies

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 resubmission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 Add new indication as follows:

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
DURVALUMAB Injection	NEW (Public) NEW (Private)	1,500 mg	5
Available brands			
Imfinzi (durvalumab 500 mg/10 mL injection, 10 mL vial) (durvalumab 120 mg/ 2.4 mL injection, 2.4 mL vial)			
Restriction Summary New 1			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒ Medical Practitioners		
	Restriction type: ☒ Authority Required (STREAMLINED)		
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		

	Severity: Locally advanced, metastatic or recurrent
	Condition: Biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer)
	Indication: Locally advanced, metastatic or recurrent biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer)

	Patient population:
	Patient must have either of the following at treatment initiation: (i) locally advanced biliary tract cancer that is untreated with systemic anti-cancer therapy in the unresectable setting, (ii) metastatic biliary tract cancer that is untreated with systemic anti-cancer therapy in the metastatic setting;
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 1 at treatment initiation with this drug
	AND
	Clinical criteria:
	The treatment must be/have been initiated with both: (i) gemcitabine, (ii) cisplatin (refer to Product Information of gemcitabine and cisplatin for dosing information)
	AND
	Patient must not have developed disease progression while being treated with this drug for this condition

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

The sponsor had no comment.