

7.13 TRIFLURIDINE with TIPIRACIL

tablet, 15 mg trifluridine with 6.14 mg tipiracil, 20 mg trifluridine with 8.19 mg tipiracil, LONSURF[®], Servier Laboratories (Australia) Pty Ltd

1 Purpose of Application

- 1.1 The minor submission sought an Authority Required (STREAMLINED) listing for trifluridine with tipiracil (thereafter referred to as trifluridine/tipiracil) for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy.

2 Requested listing

- 2.1 The submission requested the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
TRIFLURIDINE + TIPIRACIL					
Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20	3	0	\$ [REDACTED] ^a	LONSURF	Servier Laboratories
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20	4	0	\$ [REDACTED] ^b		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Initial treatment

Public Summary Document – July 2017 PBAC Meeting

Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have a WHO performance status of 1 or less,</p> <p>AND</p> <p>Patient must have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent, OR</p> <p>Patient must not be a candidate for treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapies, anti-VEGF agents and anti-EGFR agents.</p>
Administrative Advice	<p>The prescribed dose is not permitted to be increased once it has been reduced.</p> <p>No increase in maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p>

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition,</p> <p>AND</p> <p>Patient must not have progressive disease while on this drug,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.

Administrative Advice	<p>The prescribed dose is not permitted to be increased once it has been reduced.</p> <p>No increase in maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p>
------------------------------	---

^a Effective price = \$ [redacted] (including [redacted] % rebate)

^b Effective price = \$ [redacted] (including [redacted] % rebate)

- 2.1 In contrast to the March 2017 resubmission, the minor submission (p4) requested that the listing for trifluridine/tipiracil not permit prescribing of any repeats to allow the dosage and timing of the next cycle to be tailored to individual patients and prevent continued use in patients with disease progression.

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

3 Background

- 3.1 A major submission for trifluridine/tipiracil was previously considered by the PBAC at the November 2016 meeting. The major submission was made under the TGA/PBAC parallel process. The TGA clinical evaluator’s first round report was received prior to the November 2016 PBAC meeting.
- 3.2 At the November 2016 meeting, trifluridine/tipiracil was not recommended for listing on the basis of a modest clinical benefit, high and uncertain incremental cost-effectiveness ratio, and concern that the extent of benefit as observed in the clinical trial would not be realised in clinical practice (November 2016 Public Summary Document (PSD) paragraph 7.1).
- 3.3 Trifluridine/tipiracil was again considered at the March 2017 PBAC meeting where it was not recommended for listing. While the PBAC noted the revised lower incremental-cost effectiveness ratio (ICER) presented, it considered that the ICER remained high and uncertain as concerns regarding the modest benefits observed in clinical practice remained (March 2017 PSD, paragraph 5.1). Further, the PBAC considered that the proposed rebates of [redacted] % and [redacted] % for utilisation over the financial caps were insufficient to address the significant financial impact to the PBS (March 2017 PSD, paragraph 5.8).
- 3.4 A summary of the November 2016 major submission, March 2017 minor resubmission and July 2017 minor resubmission is presented in Table 1.

Public Summary Document – July 2017 PBAC Meeting

Table 1: Summary of November 2016 major submission, March 2017 minor resubmission, and July 2017 minor resubmission

	November 2016 major submission	March 2017 minor resubmission	July 2017 minor resubmission
Requested PBS listing	Authority Required (STREAMLINED) listing for the treatment of patients with mCRC who have been treated with/not considered candidates for available therapies.	Requested either an Authority Required or Authority Required (STREAMLINED) listing PBAC Comment: (paragraph 2.2) The PBAC considered the risk of leakage to indications other than mCRC to be small and that a STREAMLINED authority may be acceptable.	Authority Required (STREAMLINED) listing for the treatment of patients with mCRC who have been treated with/not considered candidates for available therapies.
Requested effective DPMQs	Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20: \$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20: \$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	*Prices include [REDACTED] % rebate	*Prices include [REDACTED] % rebate	*Prices include [REDACTED] % rebate
Main comparator	Best supportive care PBAC Comment: (paragraph 7.4) The PBAC considered best supportive care to be the appropriate comparator.	No change	No change
Clinical evidence	Primary trial: RECOURSE (n=800), head to head, randomised double blind trial (used in economic model) Supportive trial: J003 trial (n=169), considered supportive because of Asian ethnicity of recruited patients (not used in economic model as required ECOG data not reported) PBAC Comment: (paragraph 7.5) the results of the J003 trial were similar to those for the RECOURSE trial.	Pooled analysis of RECOURSE and J003 trials used in economic model as revised model based on PFS which was reported in both trials	No change from March 2017
Key effectiveness data	RECOURSE trial <u>Mean overall survival, months (95% CI)</u> trifluridine/tipiracil: 9.7 (9.2, 10.3); placebo: 7.2 (6.6, 7.9) difference: 2.5 months <u>Mean time to deterioration of ECOG-PS to ≥2, months (95% CI)</u> trifluridine/tipiracil: 6.5 (6.1, 6.9), placebo: 4.8 (4.3, 5.3) difference: 1.7 months	Pooled RECOURSE and J003 trials <u>Mean overall survival, months</u> trifluridine/tipiracil: 10.0, placebo: 7.4, difference: 2.6 <u>Mean progression-free survival, months</u> trifluridine/tipiracil: 3.7, placebo: 1.9, difference: 1.8 months	No change from March 2017
Clinical claim	Superior in terms of efficacy and inferior in terms of safety to best supportive care (placebo). PBAC Comment: (paragraphs 7.5, 7.6	No change PBAC Comment: (paragraph 5.5) The PBAC considered the magnitude of the benefit to be	No change

Public Summary Document – July 2017 PBAC Meeting

	November 2016 major submission	March 2017 minor resubmission	July 2017 minor resubmission
	and 7.8) <u>Efficacy</u> : claim of superior efficacy adequately supported by the data, although the magnitude of the benefit was modest and may not be realised in clinical practice. <u>Safety</u> : claim of inferior safety was reasonable. The toxicity associated with trifluridine/tipiracil was predictable, with myelosuppression being the key adverse event.	modest. The PBAC reiterated its previous concern that the magnitude of benefit observed in the trials may not be realised in clinical practice.	
Economic evaluation, model structure	Trial based analysis (no extrapolation) using data from RECOURSE with OS partitioned based on ECOG PS. Utility values: ECOG 0,1 = 0.81, ECOG 2,3 = 0.70 (based on transformation of ECOG-PS scores, data not specific to mCRC) PBAC Comment: (paragraph 7.9) a model which defined health states based on progression would be more informative, in part because such a model could be populated using utility values specific for mCRC patients.	Trial based analysis (no extrapolation) using data from RECOURSE and J003 with OS partitioned based on PFS. Utility values: pre-progression = 0.75, post-progression = 0.59. Based on regorafenib mCRC trial with a 2.5% increase (from 0.73 to 0.75) to the pre-progression value to account for better safety profile of trifluridine/ tipiracil compared to regorafenib.	No change from March 2017
Economic evaluation, results	Incremental costs: \$ Incremental time with ECOG of 0 or 1: 0.14 years Incremental life years: 0.21 Incremental QALYs: 0.16 ICER: <ul style="list-style-type: none"> \$45,000 – \$75,000 per LY gained \$75,000 – \$105,000/QALY gained 	Incremental costs: \$ Incremental PFS: 0.15 years Incremental life years: 0.22 Incremental QALYs: 0.15 ICER: <ul style="list-style-type: none"> \$15,000- \$45,000per LY gained \$45,000 – \$75,000/QALY gained (\$45,000– \$75,000 using unadjusted utility value of 0.73 for progression-free). PBAC Comment: (paragraph 5.7) The PBAC considered the base case ICER of \$45,000 – \$75,000/QALY gained presented in the resubmission to be unacceptably high and uncertain given concerns over the likely modest benefits observed in clinical practice.	Incremental costs: \$ Incremental PFS: no change Incremental life years: no change Incremental QALYs: no change ICER: <ul style="list-style-type: none"> \$15,000 - \$45,000 per LY gained \$45,000 – \$75,000/QALY gained(using unadjusted utility value of 0.73 for progression-free)
Number of patients and estimated net cost to PBS	Patient numbers: Year 1: , Year 5: Net PBS cost: Year 1: \$20 – \$30 million , Year 5: \$30 – \$60 million	Revised financial estimates not presented in the pre-PBAC response. The sponsor maintained that the utilisation	Uptake rate reduced from 30% of patients treated in the first-line setting for mCRC to 24% in the first

Public Summary Document – July 2017 PBAC Meeting

	November 2016 major submission	March 2017 minor resubmission	July 2017 minor resubmission
	<p>PBAC Comment: (paragraph 7.12) number of patients to be treated and the associated financial impact is likely to have been overestimated. In particular the uptake of trifluridine/tipiracil was considered to have been overestimated as to be suitable for treatment patients are required to be fit and healthy with a good performance status despite having received a number of previous treatments for their mCRC.</p>	<p>estimates in the Nov 16 submission were reasonable.</p> <p>PBAC Comment: (paragraph 5.8) The PBAC considered the estimated financial impact of more than \$100 million over 6 years to be significant. The PBAC noted that no changes to the utilisation estimates were presented in the minor resubmission compared with the original submission. The PBAC considered utilisation likely to be overestimated given the modest efficacy observed.</p>	<p>year of listing and from 36% to 28% in subsequent years</p> <p>Patient numbers: Year 1: ■■■■ Year 5: ■■■■ Net PBS cost: Year 1: \$10 – \$20 million, Year 5: \$10 – \$20 million.</p>
Risk share	Acknowledged but no details.	<p>A further ■■■% rebate (total of ■■■%) for any actual expenditure that exceeds the annual subsidisation caps by up to ■■■%. An additional ■■■% rebate (total of ■■■%) for any actual expenditure that exceeds the annual subsidisation caps by more than ■■■%.</p> <p>PBAC Comment: (paragraph 5.8) Although the PBAC considered the financial caps were unlikely to be reached, the proposed rebates of ■■■% and ■■■% were considered to be insufficient.</p>	A ■■■% rebate for any actual expenditure that exceeds the annual subsidisation caps.
Advice for resubmission	<p>PBAC Comment: (paragraph 7.13) any resubmission should include an economic model with health states based on progression, and the utility values from the regorafenib mCRC trial should be applied to these health states. The PBAC considered that the base case ICER for this scenario should not exceed \$45,000 – \$75,000/QALY gained. The PBAC stated the resubmission would need to be in the form of a major submission if substantive changes are made to the model evaluated as part of the current submission.</p>	<p>Revised model is as requested. ICER \$45,000 – \$75,000/QALY gained. Submission considers ICER to be conservative. Model changes are not substantive.</p> <p>PBAC Comment: (paragraph 5.9) any resubmission should be made subsequent to TGA approval, the benefit likely to be realised in clinical practice should be considered, and any risk share arrangement should more adequately contain the financial risk to the Commonwealth.</p>	

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; LY = life year; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year

Source: compiled from the November 2016 PBAC Minutes, March 2017 PBAC Minutes and July 2017 minor submission.

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 as it was a minor submission.

Consumer comments

4.2 The Medical Oncology Group of Australia (MOGA) reiterated its previous support for the trifluridine/tipiracil submission. It was noted that the indication for this item represents an area of unmet need after failure of standard prior therapies and trifluridine/tipiracil has a proven survival benefit in a phase 3 trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for trifluridine/tipiracil, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) , based on a comparison with placebo.

Clinical trials

4.3 As a minor submission, no clinical trials were presented in the resubmission.

Economic analysis

4.4 As per the March 2017 resubmission, the minor resubmission presented a trial-based economic evaluation. There were no structural changes to the economic model presented in the March 2017 resubmission.

4.5 This minor resubmission made the following revisions to the economic evaluation presented in the March 2017 minor resubmission:

- Increased the proposed rebate on the dispensed price for maximum quantity to [REDACTED] % from [REDACTED] %.
- Corrected the wholesaler margin (7.52% of the ex-manufacturer price up to \$69.94) so that it was to be calculated for the maximum quantity instead of per pack. The updated dispensing fee of \$7.02 was also applied.

4.6 A summary of the outcomes of the revised economic analysis are presented in Table

2 below.

Table 2: Results of the economic analysis

	Trifluridine/tipiracil arm	Placebo arm	Increment
Costs			
Average total drug costs	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Average cost per patient to manage AEs	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Clinician visits	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Monitoring costs	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Total costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Outcomes			
Mean OS (in months)	10.0	7.4	2.6
Mean OS (in years)	0.84	0.62	0.22
Mean QALYs	0.54	0.39	0.15
Incremental cost of trifluridine/tipiracil vs placebo per LY gained:			\$ [REDACTED]
Incremental cost of trifluridine/tipiracil vs placebo per QALY gained:			\$ [REDACTED]

Abbreviations: AE = adverse event; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year
Source: Table 2, page 13 of the minor resubmission.

- 4.7 The revised economic analysis, which incorporates the proposed [REDACTED] % rebate, resulted in a base case ICER of \$45,000 - \$75,000/QALY gained.
- 4.8 The revised economic analysis applied the same adjusted utility value for the progression free health state (0.73) as per the March 2017 minor resubmission. When the unadjusted utility value for the progression free health state from the CORRECT (regorafenib) trial was applied in the model (0.73), the ICER increased to \$45,000 - \$75,000.

Drug cost/patient/course: \$ [REDACTED]

- 4.9 The submission stated (p13) that the average effective dispensed cost per patient per cycle (one month) is \$ [REDACTED], estimated based on an average dose of 60 mg, and the effective dispensed price for 3 packs of 20 tablets of the 20 mg strength. However, the submission's excel workbook showed that the average effective dispensed price per patient per cycle to be \$ [REDACTED]. The submission stated that based on a per cycle cost of \$ [REDACTED] and an average 3.42 cycles of treatment per patient, the total effective dispensed cost would be \$ [REDACTED].
- 4.10 The Secretariat noted the drug cost per patient per course in the March 2017 minutes was lower (\$ [REDACTED]), however this was based on 3 rather than 3.42 cycle of treatment (i.e \$ [REDACTED] x 3). (March 2017 PSD paragraph 4.17).

4.11 The Pre-Sub-Committee Response (PSCR)(p2) argued that the cost per patient per course of \$ [REDACTED] (calculated by averaging the total drug costs per course per patient) was correctly calculated in the submission. The PSCR did not address the discrepancy between the average effective dispensed price per patient per cycle in the submission (\$ [REDACTED]) and the submission’s excel workbook (\$ [REDACTED]).

Estimated PBS usage & financial implications

4.12 At its November 2016 meeting, the PBAC considered that the submission’s estimate of the number of patients to be treated was likely to have been overestimated. In particular, the uptake of trifluridine/tipiracil ([REDACTED]% in Year 1 in patients who have received first and second line treatments for mCRC, followed by [REDACTED]% each year thereafter) was considered to have been overestimated, as to be suitable for treatment, patients are required to be fit and healthy with a good performance status despite having received a number of previous treatments for their mCRC (November 2016 PSD, paragraph 7.12). The March 2017 minor resubmission made no changes to the estimates of utilisation. The current minor resubmission revised the uptake rate for trifluridine/tipiracil from [REDACTED]% to [REDACTED]% in Year 1 and from [REDACTED]% to [REDACTED]% in subsequent years. The submission’s revised estimated PBS usage and financial implications are shown below in Table 3 below.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Likely number of patients in each year	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 15 mg x 20 x 1 pack per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 15 mg x 20 x 2 packs per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 15 mg x 20 x 3 packs per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 20 mg x 20 x 1 pack per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 20 mg x 20 x 2 packs per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 20 mg x 20 x 3 packs per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of patients receiving 20 mg x 20 x 4 packs per cycle	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Average number of cycles of treatment per patient	3.42					
Total dispensed cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Public Summary Document – July 2017 PBAC Meeting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total rebates paid	-\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]
General patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Concessional patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net financial implications for PBS budget	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 3, page 14 of the minor resubmission.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$10 – \$20 million.

4.13 The estimated PBS usage and financial implications presented in the minor resubmission have not been evaluated.

4.14 At its October 2016 meeting, the ESC was uncertain of whether a decline in the first-line mCRC population from mid-2013 to 2015 presented in the November 2016 major submission was the result of the submission’s method or if it was a real trend in PBS use (November 2016 PSD, paragraph 6.41). Actual PBS data to December 2015 was presented in the financial estimates. It was noted that the minor resubmission did not address the ESC’s concern regarding the continuing decline of the first-line mCRC population and assumption of continuing linear growth in treated patients. However, it was noted that while the growth rates were highly variable, the average growth from January 2011 to January 2015 is similar to the submission’s assumption (7.6% vs 7.4%, respectively).

4.15 The revised financial estimates incorporated the proposed [REDACTED]% rebate on the dispensed price for maximum quantity. The estimated net cost to the PBS was \$10 – \$20 million in Year 6 of listing, with a total net cost to the PBS of approximately \$60 – \$100 million over the first 6 years of listing.

Financial Management – Risk-sharing Arrangements

4.16 The minor resubmission proposed a rebate of [REDACTED]% for any expenditure that exceeds the annual subsidisation caps which correspond to the estimated net cost to the PBS.

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

5 PBAC Outcome

- 5.1 The PBAC did not recommend the listing of trifluridine with tipiracil on the PBS for treatment of patients with metastatic colorectal cancer (mCRC) who have been treated previously with or are not considered suitable for current available therapies. The PBAC based its decision on a modest clinical benefit in the context of substantial toxicity, and high and uncertain incremental cost-effectiveness ratio given the extent of benefit observed in the trial and model may not be realised in clinical practice.
- 5.2 The PBAC noted that the Medical Oncology Group of Australia (MOGA) reiterated its support for the trifluridine/tipiracil submission, and based on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) the rating was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).
- 5.3 The PBAC reiterated its view that as metastatic cancer is rarely cured and treatments aim to relieve symptoms or delay death, there will always be an unmet clinical need for additional effective and well-tolerated therapies.
- 5.4 The PBAC recalled that the median increase in PFS of 0.3 months (HR 0.49; CI: 0.42, 0.58) compared with best supportive care in the RECURSE trial (n=800) was small and that the majority of patients (i.e. 53% of patients in the trifluridine/tipiracil treatment arm and 79% of patients in the best supportive care arm) had progressed by week 8. The PBAC also recalled that the median gain in OS was 2.0 months (HR 0.69; CI: 0.59, 0.81) in the RECURSE trial was modest, and that a substantial proportion of the estimated gain in overall survival was in the post-progression state associated with poorer quality of life. The PBAC also recalled that the results of the J003 trial (n=169) were similar to those of the RECURSE trial.
- 5.5 The PBAC noted that the reduced price for trifluridine/tipiracil based on a [REDACTED] % rebate was incorporated into the economic model from the March 2017 resubmission. This decreased the ICER from \$45,000 – \$75,000 per QALY gained to \$45,000 – \$75,000 per QALY gained.
- 5.6 The PBAC recalled that at its November 2016 meeting, it considered that the base case ICER should not exceed \$45,000 – \$75,000 per QALY gained. The PBAC considered that the base case ICER presented in the submission likely represents a best case scenario where the benefit observed in the trial setting is reflected in clinical practice and the true ICER would be higher than \$45,000 – \$75,000 per QALY and therefore not cost-effective at the price proposed. The PBAC advised that a significant price reduction would be required to address its concern about the modest clinical benefit and the impact this has on the cost-effectiveness.

- 5.7 The PBAC noted that 9.4% of patients in the RECURSE trial received granulocyte colony stimulating factors (GCSF) which would not be routinely used in Australian clinical practice. The PBAC considered that in clinical practice, neutropenia would likely lead to dose reductions and delays which would impact on efficacy (November 2016 PSD, paragraph 7.8). The March 2017 resubmission claimed that if dose reductions and delays occurred, it would result in lower costs of trifluridine/tipiracil and that the costs of administering GCSF would not be incurred. The minor resubmission further argued that if efficacy and costs are simultaneously reduced then the impact on the ICER is likely to be minor. The PBAC noted that the sponsor had not provided any information to support these arguments. The PBAC considered that incorporating the cost of GCSF into the economic model did not adequately address its concerns about the likely cost-effectiveness with the use of trifluridine/tipiracil in clinical practice.
- 5.8 The PBAC noted that the submission reduced the uptake rate (of patients treated in the first-line setting for mCRC) from ■■■% to ■■■% in the first year after listing and from ■■■% to ■■■% in subsequent years. The PBAC considered that the revised utilisation was more likely to reflect actual uptake. The PBAC noted that the reduced uptake rate together with the increased rebate of ■■■% resulted in an estimated net financial impact of \$60 – \$100 million over 6 years. The PBAC considered that while this was a reduction from the estimated financial impact of more than \$100 million over 6 years in the March 2017 submission, the financial impact of listing was still significant.
- 5.9 The PBAC considered that the sponsor’s request for no repeats to be permitted in the proposed listing for trifluridine with tipiracil was inappropriate noting that this would impose undue burden on clinicians and lacks precedent for other PBS-listed oral antineoplastic agents with similar toxicity profiles.
- 5.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view

about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7 Sponsor's Comment

Servier will continue to work with the PBAC to achieve, if possible, PBS-listing for trifluridine with tipiracil, as there is a high unmet need for patients. A minor resubmission will be considered at the November 2017 PBAC meeting.